DISSERTATION

ON

A STUDY ON PROGNOSTIC SIGNIFICANCE OF QT_C INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS

DISSERTATION SUBMITTED TO

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CERTIFICATE

This is to certify that this dissertation entitled

"A STUDY ON PROGNOSTIC SIGNIFICANCE OF QT_C INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS"

is the bonafide original work of **Dr.M.BALAMURUGAN** in partial fulfilment of the requirements for M.D Branch -I (General Medicine) Examination of the TamilnaduDr. M.G.R. Medical University to be held in APRIL - 2015. The period of study was from October– 2011 - November 2012.

Prof. Dr. S.MANOHARAN , M.D.,
Unit Chief M-6
Department of Internal Medicine,
Thanjavur Medical College.

Prof.Dr.P.G.SANKARANARANAN
Head of the Department,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

Prof. Dr.MAHADEVAN M.S.,

DEAN

Thanjavur Medical College,

DECLARATION

I, **Dr.M.BALAMURUGAN**, solemnly declare that the dissertation titled DISSERTATION ON **"A STUDY ON PROGNOSTIC SIGNIFICANCE OF QT_C INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS"** is a bonafideworkdone by me at Thanjavur Medical College, Thanjavur during Januuary 2014 – september 2014 under the guidance and supervision of **Prof. Dr. S.MANOHARAN , M.D.,** Unit Chief M-6, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to TamilnaduDr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. degree (Branch -I) in General Medicine**.

Place: Thanjavur.

Date: . **Dr.M.BALAMURUGAN**

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CONTENTS

A STUDY ON PROGNOSTIC SIGNIFICANCE OF QTc INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS.

BACK GROUND:

Thanjavur being the rice bowl of Tamilnadu which is surrounded by numerous villages the use of pesticides particularly OPC are higher here. So it is a ideal place to study the clinical profile and prognostic factors in OPC poisoning.

In OPC poison apart from respiratory failure, cardiotoxicity also plays a major part in determining the mortality .Though the exact pathophysiology has not been studied, we are analyzing one such manifestation of cardiotoxicity as a predictor of mortality.

AIMS AND OBECTIVES:

To calculate the QTc interval in the initial ECG before atropinization and to correlate with outcome of the patient.

MATERIALS AND METHODOLOGY:

70 Patients admitted in thanjavur medical college with history of OPC poisoning with container were taken for our study. Relevant Clinical examination done and recorded. A 12 lead ECG taken before treatment. QTc interval calculated using Bazzets formula.Results analysed statistically.

RESULTS:

Most of the patients in our study group are males with suicide being the common cause. In our place monochrotophos and chlorpyriphos are the common compounds encountered.

We classified our group in to those having normal, intermediate and prolonged QTc. 62% had prolonged QTc interval.

Among the total 12 death 9 (75%) belong to the group with prolonged QTc. There is a statistically significant difference in mortality. So QTc interval definitely has a significant prognostic value in OPC poisoning.

CONCLUSION:

So early detection of QTc prolongation in ECG and initiation of early intensive treatment for OPC poisoning may reduce the mortality.

Key words : OPC- organophosphorus poisoning ; QTc - corrected QT interval

INTRODUCTION

India being one of the most developing country with numerous scientific technologies but still having agriculture as its backbone. So even with lot of developments in various fields of agriculture the use of pesticide is a must in all stages of agriculture.

But the sad part of it is in our country the pesticide use meant not only to kill pests but also taking out many of human life [2], in the form of suicidal ,accidental or homicidal poisoning. Incidence of poisoning by pesticides has been increasing in recent decades. Insecticides are the most commonly used pesticides in the developing countries[1].

WHO estimates that there are about 3 million pesticide poisoning cases reported annually with relatively increased cases reported in developing countries like India.

Among pesticides, Organophosphorus is the most common cause of acute poisoning. Among the different mode of poisoning, suicidal poisoning is the commonest in developing countries.

Even though definitive antidote is available for OPC poisoning the mortality rate is quite high when compared to other pesticide for which there is no specific antidote. There are various prospective trials in comparing the different

prognostic factors between death and survival groups of organophosphorus poisoning.

Most of the important factors like the duration of ventilator use, dose and duration of atropine needed ,level of urine organophosphate[3] and duration it was being excreted were similar in both groups.

Almost all these parameters indirectly reflect the enhanced muscarinic and nicotinic activities , apart from this cardiotoxicity is also a part of OPC toxicity[4].

One such parameter reflecting this is QTc interval in OPC poisoning before atropinisation.

In the absence of traditionally used prognostic marker like serum cholinesterase which is little bit costlier, Electrocardiogram which is available in every health care level can be used as a comparable prognostic indicator.

Here in Thanjavur which is called to be Rice bowl of Tamil Nadu is surrounded by villages & villagers ,where plenty of person will be handling with this pesticide ,it is a ideal place for conducting a study in OPC poisoning. So my topic will be a study comparing the outcome of OPC poisoning with the help of initial ECG taken before atropinisation.

AIMS & OBJECTIVES

1 . To correlate their QTc interval in the initial ECG with the outcome.

2 . To evaluate the clinical profile of patients admitted for OPC poisoning.

So the main aim is to found out whether QTc prolongation can be used as a prognostic indicator for OPC poisoning based on their clinical presentation.

HISTORICAL REVIEW.

It was M.J.B.Orfila who Modern toxicology started in 1789 – 1853 A.D .

He was a physician from Island of Minorca . He wrote the first book which totally describes the injurious effects of chemicals . He defined the toxicology and distinguished into chemical toxicology , forensic toxicology and analytical chemistry[5].

In 1831 , Mein separated and described atropine. In 1854 Clermont described TEPP [6] .TEPP is tetra ethyl pyrophosphate which is highly active. In 1867 ,Bezold and Bleobaum described the activity of atropine that blocks the cardiac manifestations of vagal stimuli . In 1914 , Dall assumed the enzyme esterase . It was later described by Nauratal and Plattner . In 1930 , Stedman gave the name as cholinesterase[7] . In 1932 Lange and Krueger synthesized dimethyl and diethyl phosphoro fluoridate . In 1946 , McCombie and Saunders described DFP [8]. DFP is diisopropyl fluoro phosphate .It was enumerated by scientists . In 1952 , Schrader described the structure required for insecticidal activity . In 1955 , Wilson and Ginsberg described 2- pyridine aldoxime[9] . It has the ability to reactivate cholinesterase enzyme when it is inhibited by organophosphorus compound.

In India , organophosphorus poisoning was initially explained by Viswanathan Et al in 1962.[10]

INCIDENCE OF ORGANOPHOSPHORUS POISONING

In 1974 , the World Health Organization estimated that around 5 lakhs cases of pesticidal poisoning occurred yearly worldwide [11]. Among this 9000 and above were died . In this deaths 99 % occurred in developing countries.[12] In 1981 , there was 750 ,000 cases . In 1983 , the number raised to 2,000,000 . Of these 40,000 deaths reported .In 1990 ,there was around 3,000,000 cases ,among which 2,000,000 fatalities reported.

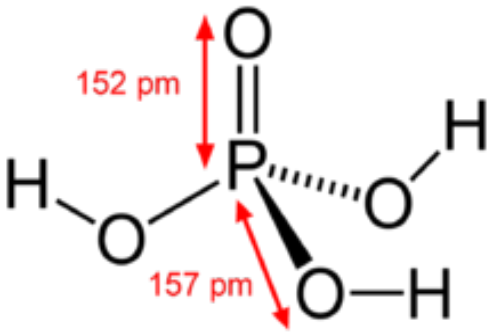
Incidence in India :

- P.G.Kamath from G.T. Hospital Mumbai ,gave report that among poisoning cases , 34% were organophosphorus poisoning.[13]
- During 1984 – 1988 , J Sunder Ram gave a report . He reported 69 % occurrence of organophosphorus poisoning among total poisoning cases.[14]
- Singh et al gave a report of 19.23% incidence . He reported it from G.B.Pant Hospital , New Delhi.[15]

CHEMISTRY[16]

OP COMPOUND

Organophosphorus has central phosphorus atom bind to oxygen atom, two alkyl group and one leaving group . The liquid form of organophosphorus are volatile, so poisoning through inhalation also occur . Other route are ingestion, dermal absorption.



Irrespective of route of entry, it diffuse into blood stream , transport to various organ system, here it move towards the nerve synapse and binds to acetylcholine esterase. After some time it depends upon the compound type organophosphorus-esterase bonds will mature through dealkylation of organophosphorus. Through maturation the bond become irreversible leading to destruction of both organophosphorus and acetylcholine esterase .

Organophosphorus compounds are categorized into two groups:

1. Alkyl phosphates – they are direct inhibitors.

- Example. Malathion.
- They manifest as acute cholinergic crisis.
- They do not manifest as delayed type of weakness.
- The response to atropine is very quick.

.2. Arylphosphates – they are indirect inhibitors.

- Example. Parathion.
- They do not manifest as acute cholinergic crisis.
- But they develop severe persistent fasciculations.
- They manifest as delayed type of weakness.
- The response to atropine is not rapid and the requirement is high.

PHYSICAL & CHEMICAL PROPERTIES OF INDIVIDUAL COMPOUNDS

MONOCROTOPHOS:[17,18]

One of the highly hazardous organophosphorus compound available in india is monocrotophos.it is an easily affordable and widely used in India.

Monocrotophos poisoning occur most frequently as suicidal as well as accidental poisoning.

Apart from being a insecticide it is also an acaricide. Vinyl phosphate group in its structure make it more toxic. In agricultural fields it is very useful to controls pests on cotton, rice and sugarcane. It is highly toxic irrespective of the modes of exposure like ingestion ,inhalation and skin exposure.

Oral intake of 1200mg of monocrotophos is fatal to human being(according to Hayes and Laws 1993).WHO classified this compound as Class 1b i.e highly hazardous.

CHOLORPYRIFOS[19]

It is o-o-diethyl o-(3,5,6-trichloro-2 pyrinidyl)-phosphorothioate. It is one of the broad spectrum cholirinated organophospate insecticide and accaricide. it is also a nematocide.it appears as white colored solid crystals with a mercaptan smell i.e smells like sulfur compounds present rotten eggs, onion, garlic and skunk.It has solubility of 1.4mg/dl at 25 degree C.

Cholorpyrifos cause inhibition of both enzymes Neuropathy target esterase and Cholinesterase .Compared to other compounds the inhibition of NTE is more so chances of intermediate syndrome and delayed neuropathy are common.

PHORATE[20]:

It is o,o-Diethyl s-ethylthiomethyl phosphorodithioate .It is a non-biocumulative broad spectrum organophosphorous acaricide,insecticide. It is clear ,pale yellow

mobile liquid with freezing point of -42.9. At room temperature phorate is stable for 2 years in media between of pH of 5-7.

As with almost all compounds it is toxic by all routes of exposure. It is highly toxic to mammals and other non target organism. Phorate has no residual action. Most commonly used as granular formulation.

PARATHION: Pure parathion is pale yellow in color, has smell of garlic ,insoluble in water.

AZAMETHIOPHOS: It is a phosphorothiotic acid. Azamethiophos is orange yellow granules or gray to white crystalline powder. It is primarily used for fly control.

DIAZINON: Diazinon is an o-odiethyl o-ester. It is an insecticide ,used to kill the cockroaches, ants and fleas. It has low persistence in soil, half life of 2-4 weeks.

Toxic profile is comparatively less.

MALATHION: Malathion is introduced in 1950.It is Diethyl thiobutanedioate.

It is clear,brown to colourless liquid with garlic odour. It is a broad spectrum insecticide . It is used for control of sucking and chewing insecticide. Has half life of 1-25 days. In air it is rapidly degraded and has half life of one and days.

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM:

Two major division[21] are

1. Sympathetic (Thoraco lumbar)
2. Parasympathetic (Craniosacral)

Both division originate in nuclei within the CNS and exit from brain stem or spinal cord that give preganglionic efferent fibers and terminate in motor ganglia. Preganglionic sympathetic fibers exit through thoracic and lumbar spinal nerve. Parasympathetic preganglionic fibers through third, seventh, ninth tenth cranial nerve & second ,third and fourth sacral spinal nerve roots.

Preganglionic sympathetic fiber are short and terminate in ganglia located at paravertebral chain[22].

Sympathetic preganglionic fibers end in prevertebral ganglia. From ganglion Postganlionic fibers arise and innervate the target organ. Some of preganglionic parasympathetic fibers end in ganglion located outside the organ.

eg: Ciliary, Submandibular and Pterygopalatine ganglion, several pelvic ganglia. But most of Preganglionic parasympathetic fibers end in ganglion on the organ.

ENTERIC NERVOUS SYSTEM(ENS) :

It is highly organized and large collection of neuron in the of the gastrointestinal tract. It is also called as third division of ANS. It is extend from esophagus to distal colon, control both motor and sensory activity of the gut. It includes myentric plexus of Auerbach and Submucous plexus of Meissner. It control motility and secretory cells in the mucosa . ENS function as semiautonomous manner .It utilize motor outflow of ANS for modulation of gastrointestinal motility and sensory information back to CNS.

CHOLINOCEPTORS[22]:

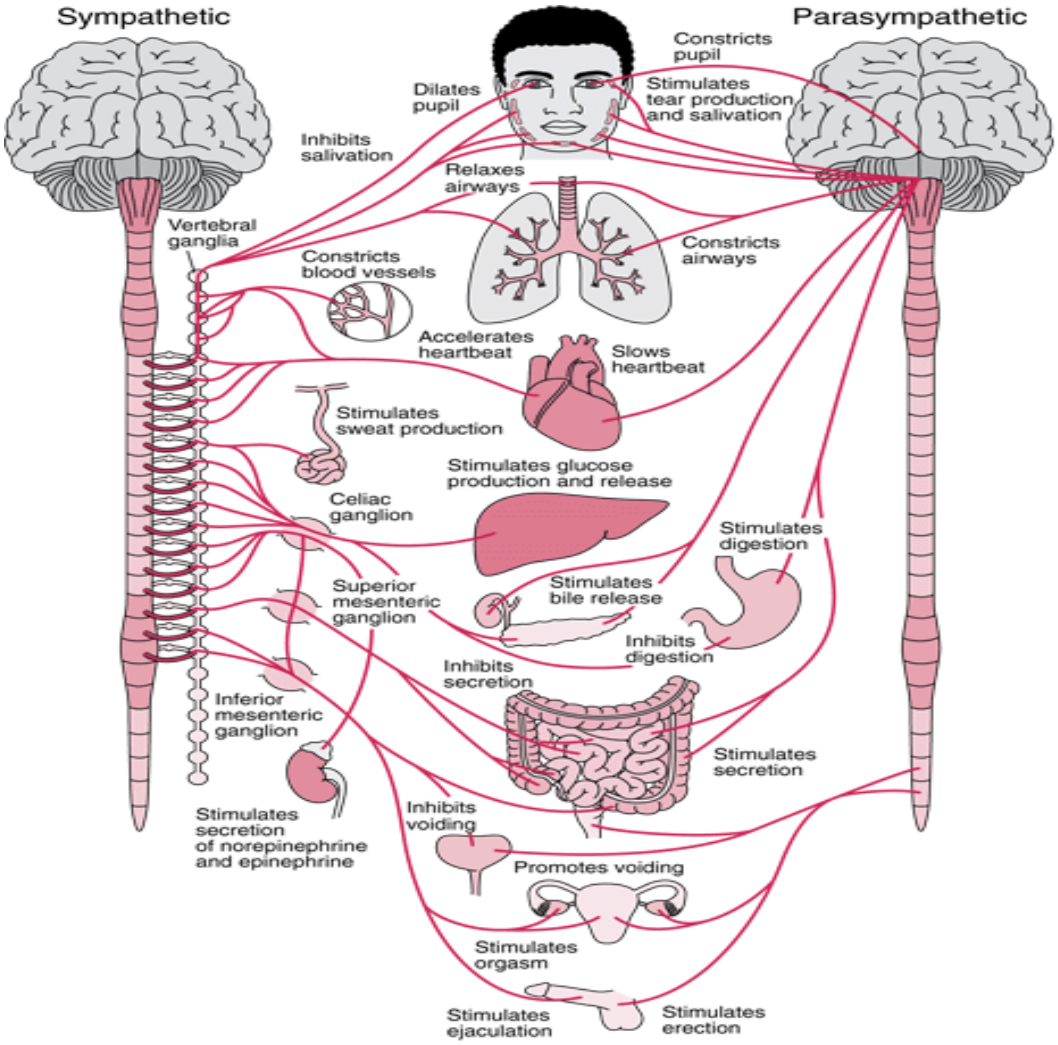
Acetylcholine has two receptor-muscarinic receptor, nicotinic receptor. Muscarinic receptor is G protein coupled receptor, nicotinic receptor is a ligand gated channel.

MUSCARINIC RECEPTOR:

These are selectively stimulated by muscarine and blocked by Atropine. It present primarly on heart, blood vessels, eye, smooth muscle, glands of gastrointestinal, respiratory and urinary tract, sweat glands and CNS .Also present in autonomic ganglia which play a modulator role.

Muscarinic autoreceptors are present prejunctionally on postganglionic cholinergic nerve endings its activation inhibit Ach release.

All blood vessels have muscarinic receptors on the endothelium but lack cholinergic innervations .On endothelial cells activation which release EDRF which diffuses to the smooth muscle and cause relaxation.

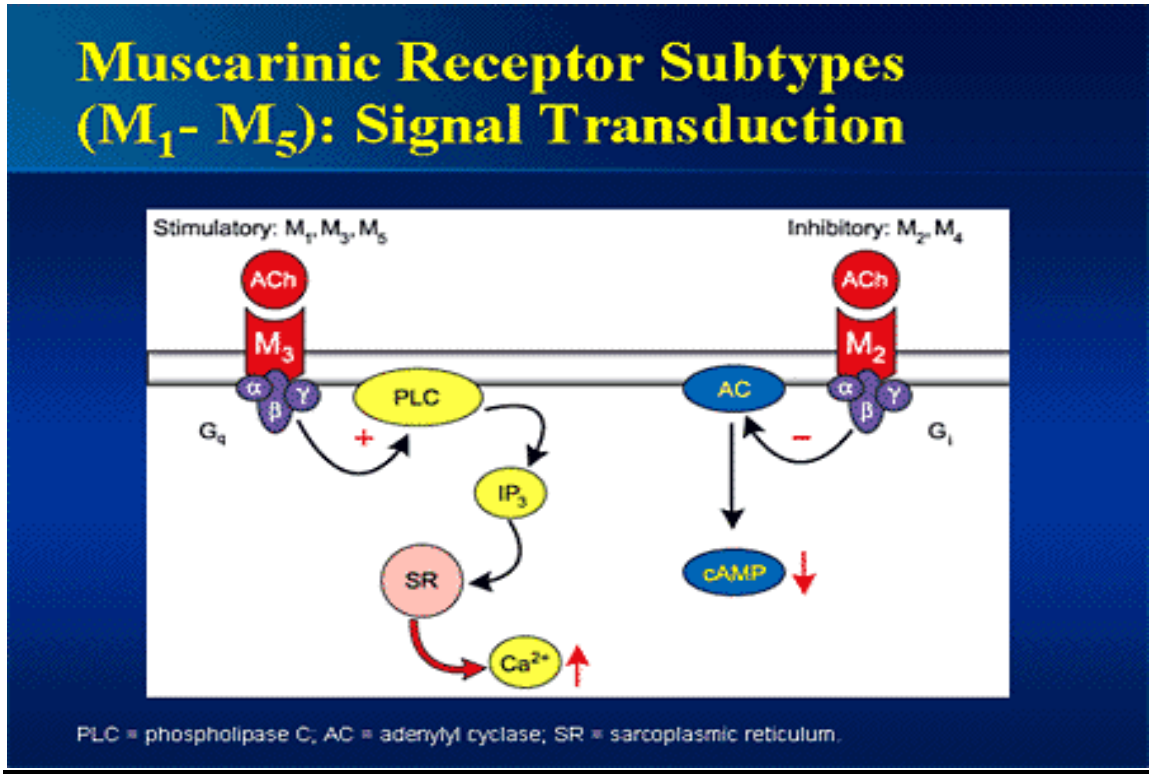


SUBTYPES OF MUSCARINIC RECEPTORS[22]:

It has 5 subtypes M1,M2, M3, M4,M5.

M1,M2,M3 are major subtypes. M4 and M5 are present mainly on nerve ending in brain and modulate the release of neurotransmitters.

MECHANISM OF ACTION IN RECEPTOR LEVEL:



M1 receptor:

It is a G protein coupled receptor located on autonomic ganglia, gastric glands, CNS cause depolarization, histamine release, and learning memory and motor function respectively.

It act through IP3/DAG second messenger leads to increased cytosolic calcium, activation of phospholipase A2 cause increased prostaglandin synthesis.

Agonist of M1 receptor: Oxotremorine,MCN-343A

Antagonist of M1 receptor: Pirenzepine and Telenzepine

M2 RECEPTOR:

It is also G protein coupled receptor. Act by potassium channel opening, decreases the cyclic AMP.

Present on SA node , activation of which cause hyperpolarization ,decreased rate of impulse generation; AV node- decrease the velocity of conduction; Atrium- shortening of APD duration, decrease the contractility; in ventricle- also it decrease the contractility .

CNS cause tremor, analgesia, visceral smooth muscle contraction .

Agonist : Methacholine

Antagonist: Methoctramine, Tripitramine .

M3 RECEPTOR: Acts via G protein coupled receptor mechanism same as M1 receptor. It is present in visceral smooth muscle, ciliary muscle, iris, exocrine glands and vascular endothelium release NO cause vasodilatation .

Bethanechol is a agonist

Darifenacin is a antagonist.

NICOTINIC RECEPTOR:

Nicotinic receptors are selectively activated by nicotine.

Antagonized by Tubocurarine and Hexamethonium.

Activation cause opening of the channel and rapid flow of cations , depolarization ,an action potential.

NM receptor:

Present in skeletal muscle endplate , mediate skeletal muscle contraction.

Phenyltrimethyl ammonium is a agonist, tubocurarine is a antagonist.

NN receptor:

Present on ganglionic cells, adrenal medulary cells, and spinal cord ,some areas of brain.

Dimethyl phenyl piperazinium is a agonist. Hexamethonium is a antagonist.

ADRENOCEPTOR:

It is classified in to Alpha and beta receptor.

These are membrane bound G-protein coupled receptors which act by modulating intracellular levels of second messenger cAMP or IP3/DAG.

ALPHA RECEPTOR: It is divided in to 2 types

ALPHA 1 RECEPTOR:

Present post junctionaly on genitourinary smooth muscle cause contraction; glands-secretion; gut-relaxation; liver-glycogenolysis; heart-arrythmia.

Phenylephrine, Methoxamine are selective agonist.

Prazosin is selective antagonist.

ALPHA2 RECEPTOR:

It is present prejunctionally in nerve ending and postjunctionally in brain pancreatic beta cells, extrajunctionally in platelets and in certain blood vessels .stimulation of this receptor cause inhibition of transmitter release, decreased central sympathetic outflow, vasoconstriction, decreased insulin release and platelet aggregation .

Clonidine is selective agonist, Yohimbine is selective antagonist.

BETA ADERNOCEPTORS:

It is divided in to Beta1, Beta2, Beta3 receptors.

BETA 1 RECEPTOR:

Present in JG cells in kidney and in heart.

Dobutamine is selective agonist. Metiprolol and Atenolol are antagonist.

BETA 2 RECEPTOR:

Present in bronchi ,blood vessels, uterus, liver ,G.I. tract, urinary tract and eye.

Salbutamol is a selective agonist.

Propranolol is a Selective antagonist.

BETA 3 RECEPTOR:

Present in adipose tissue.

CLINICAL FEATURES

The clinical features of OPC poisoning as described is mainly due to excess of acetylcholine which acts on both of its receptor and produce a syndrome that mimic like parasympathetic over activity syndrome.

Sequential triphasic illness that has been described in OPC poisoning includes

- Acute cholinergic phase
- Intermediate syndrome
- OPIDN (OP induced delayed polyneuropathy)

CHOLINERGIC PHASE:

The clinical features can be classified simply as

1. Muscarinic features
2. Nicotinic features (Wadia type-2 syndrome) [23]
3. Central nervous system (CNS) features [23]

MUSCARINIC MANIFESTATIONS:

Otherwise called as (Wadia type-1 syndrome)

Characterized by

- Cardiovascular – decreased pulse rate & BP
- Respiratory[25] - Rhinorrhea, bronchorrhea, bronchospas, non cardiogenic pulmonary edema.
- Gastrointestinal– excessive salivation, nausea and vomiting, abdominal pain loose stools ,pancreatitis [26,27] ,sometimes fecal incontinence.
- Ocular - Blurred vision, miosis , increased lacrimation.

- Sweat glands: diaphoresis.

The above said effects are usually acute and manifest within 24-48 hours of poison consumption. Most endangering period since mortalities are more common during this period.

Bronchorrhea[25] is the usual mechanism of early mortality in OPP. The origin of this excess amount of fluid is from the secretions from the glands in the airway as such and not exudation of fluid across the alveolar-capillary membrane. These secretion causes obstruction of upper and lower airways and the deposition of these bronchial secretions into the alveolar sacs produces hypoxia which is of primary concern in the initial stages of the poisoning.

NICOTINIC MANIFESTATIONS:

- Weakness of muscles
- Hyper/hypo reflexia
- Fasciculations
- Paralysis

It is due to persistent stimulation the synchrony is lost, leading to asynchronous excitation, which first leads to fibrillation of muscle fibres then later leading to paresis/complete paralysis.

Though most of the time the patients presents with bradycardia in OPC poisoning, up to 20% patients present with tachycardia in the initial stage itself even without atropine. It is due to the nicotinic effect of the acetylcholine.

It is not known whether which manifestation will be predominate at time of presentation. So with respect to pulse rate we cannot predict the atropine response in whom nicotinic manifestation predominate.

1. Immunity :

   Parathion causes suppression of both IgM and IgG immunoglobulins.

   It suppresses the function of natural killer cell and cytotoxic T cells.

ENDOCRINE AND METABOLIC ALTERATIONS:[29,28]

Rise in plasma corticosterone level.

Rise in TSH level.

Non ketotic hyperglycemia.

Glycosuria.

Increased amylase levels

TERATOGENIC EFFECTS[30] :

Prenatal deaths.

Post natal deaths.

Congenital abnormalities – vertebral anomalies ,limb abnormalities, cleft palate polydactyly , hydroureter.

REGULATION OF TEMPERATURE :

Hypothermia.

Increased diaphoresis.

CLINICAL SEVERITY GRADING

1. WHO CLASSIFICATION FOR SEVERITY OF OPC POISONING[30]:

MILD	MODERATE	SEVERE
Anorexia Headache Dizziness Miosis Tremors of the tongue and the eyelids	Salivation , Sweating Lacrimation Urination Abdominal Cramps Muscular Tremor Bradycardia.	Pin point pupils and non reactive pupils Diarrhoea Difficulty in breathing, Cyanosis loss of sphincter control convulsions heart block, coma

2. PARADENIYA GRADING OF ORGANOPHOSPORUS POISONING SCALE[31]:

It was proposed by Senanayake N (1993) for grading the severity of organophosporus poisoning. It is based on clinical manifestaion of orgnophosporus poisoning.

1.Miosis:

0 point for pupil size of more than 2mm.

One point for pupil size of less than 2mm.

Two points for pin point pupil .

2.Muscle fasciculation:

0 point for no fasciculation.

One point for presence of fasciculation but not generalized or continuous.

Two points for generalized and continuous fasciculation with central cyanosis.

3.Respiratory rate:

0 point for respiratory rate of less than 20/min.

One point for respiratory rate of more than 20/min.

Two point for respiratory rate of more than 20/min with central cyanosis.

4.Pulse rate:

0 point for pulse rate of more than 60/min.

One point for pulse rate of 41-60/min.

Two points for pulse rate of less than 40/min.

5.Level of consciousness:

0 point for conscious and rational.

One point for impaired and responds to verbal commands.

Two points for impaired and no response to verbal commands.

Add one point if convulsion present.

Total Score of 11

Score of less than 4 -mild

Score of 4-7 -moderate.

Score of more than 7 -severe.

3. **BARDIN et al.,**[32]

Proposed revised grading for OP poisoning to assess the severity.

Mild poisoning:

1.History of opc intake or exposure.

2.Mild signs : Normal consciousness

Secretion 1+

Fasciculations 1+

Severe poisoning:

Severe signs: Altered consciousness Secretions 3, Fasciculations 3+

Life threatening poisoning:

Suicide attempt ; Stupor.

Pao2 less than 75 mmHg ; Abnormal chest roentgentogram.

(1+ is mild secretion and few fasciculation, 3+is copious secretions and generalized faciculations.)

4.

5. **DREISBACHs CLASSIFICATION**[33]:

Appendix 1: Dreisbach's classification showing severity of poisoning	
Grade	**Symptoms**
Mild	Nausea, vomiting, diarrhoea, sweating
Moderate	Lacrimation, salivation, miosis, fasciculation
Severe	Incontinence, apnoeic spells, ARDS, areflexia seizures, coma

ARDS – Acute respiratory distress syndrome

INTERMEDIATE SYNDROME:

Even though the clinical features are first described by Wadia[23], he called it as type 2 paralysis. It was Senanayake[24] & Karalliedde who introduced the term

intermediate syndrome in 1987. Exact incidence has not been shown in Indian studies.

Shailesh et al , found the incidence of intermediate syndrome to be 18%.Incidence varies between 20 – 70 %. [34,35]

Because of the appearance of symptoms between the early cholinergic phase and the late onset peripheral neuropathy it is called as intermediate syndrome. Usually develops 12-96 hours after exposure to OP compound. The pathophysiology behind the development of intermediate syndrome indicates that there is a prolonged action of acetylcholine on the nicotinic receptors. It is characterized by ocular, neck, bulbar, proximal limb muscle weakness and it also leads to respiratory muscle weakness which ultimately result in respiratory failure. Sometimes dystonic posturing may be observed which may be the first clue /manifestation of this syndrome. There are no documented sensory abnormalities in this syndrome ,it remains exactly normal.

Time taken for full recovery despite prompt management will be on 4-18 days. during this stage there is a Prolonged suppression of the enzyme acetylcholinesterase and metabolites of the parent compound are excreted in urine.

Electrophysiological studies:[36] In the first few days of intermediate syndrome, shows either decrements at low frequencies of stimulation (1 to 3 Hz), with normal series at 10, 20 or 50 Hz, with normal findings at both low and 50 Hz

frequencies were recorded.. All the above said abnormalities suggest that it is a post-synaptic defect.

De-Bleecker et al [35] in a review of 19 cases of intermediate syndrome in organo-phosphorous poisoning concluded that in the early stages that CMAP showed a decremental response at lower frequencies. This responses were maximal at the second response, with gradual recovery by the ninth response, most off the time remain incomplete. Normal electromyography were recorded in the days before clinical recovery of this syndrome. According to him these abnormal findings on electromyography suggested a combination of presynaptic and postsynaptic defect.

OPIDN –Organophosphorus induced delayed neuropathy[37]

OPIDP - Organophosphorus induced delayed polyneuropathy

These both terms can be used interchangingly.

It is one of the delayed neurotoxic complication of organophosphorus compound.

Usually occurs after 5 weeks of toxin exposure. Exact cause is not known.

According to Jokanovic et al., in 2002 states that these effects are not as such due to acetyl cholinesterase by itself.

The same finding was supported by ERDMAN in 2004.

This complication is not only related to exposure of organophosphorus compounds but also seen in carbamate exposure.

HISTORY:

The ability of these compounds in causing neuropathic complication was identified in late 18th century.

It was Lorot in 1899 described six cases of multiple neuritis in patients with tuberculosis treated with preparations of "phosphocreosote" later found to have TOCP.

Later the same compound was found in adulterants of Jamaican ginger extract who suffered from similar illness in 1930s , about 600 Indians who consumed rapeseed oil contaminated with TOTP in 1988 reported a similar illness.

Many such incidences has been reported..

But not everyone who consumes this compound develop this complication. The susceptibility varies. Numerous animal studies are carried out to demonstrate the pathophysiology.

TOCP /TOTP is present not only in pesticides but also in lubricants ,fuels and other plastic industries.

Some of the neuropathy inducing OP compounds are

TOCP Tri-ortho-cresyl phosphate

TOTP	Tri-ortho-tolyl phosphate
EPN	O-ethyl O-p-nitrophenyl phenylphosphonothioate
DFP	Di isopropyl phosphorofluoridate
Leptophos	O-4-bromo-2,5-dichlorophenyl Insecticide O-methyl phenyl phosphorothioate

No specific structures or similarities has been found responsible for this neuropathic complication except for the pentavalent phosphorus atom which is attached to oxygen by a covalent coordinate bond.

NEUROPATHOLOGY:

Primary lesion involves degeneration of distal regions of large, long myelinated axons.

Later it progresses to Wallerian-like degeneration [38] of affected fiber regions.

The primary lesion usually reside in a distal non terminal axonal region, then extension of these alterations to the terminal axonal endings.

So the Regions with pathologic involvement include bilateral long peripheral nerves and of brain or spinalcord long tracts such as fasciculus gracilis, and spinocerebellar, spinolivary, rubrospinal reticulospinal tracts.

Usually Neuronal-cell bodies are spared .

MECHANISM OF TOXICITY[39]:

Even though the clinical manifestation occurs after a prolonged latent period, the first event i.e inhibition of NTE occurs within few hours.

NTE - neuropathy target esterase

Otherwise called as neurotoxicesterase.

It is a carboxyesterase enzyme (with phospholipase activity) found in both neuritic and non neuritic cells of the human body.

It is encoded in *PNPLA6* gene. Though the exact functions has not been elucidated it has its role in neural outgrowth and differentiation of neuritic tissue.

For inhibiting this enzyme the OP compound should be in its oxon form. It is not enough to just inhibit the NTE it should be significant inhibition i.e 70% to cause irreversible polyneuropathy.

The exact relationship between NTE and OPIDN has not been defined. Even though NTE is present in in non-neural cells like kidneys, lymphocytes, but no adverse effects of OP-induced inhibition of NTE have been noted outside the nervous system.

There is no correlation between the levels of NTE and clinical feature because continued NTE inhibition is not necessary for OPIDN. Activity will come back to pre-exposure levels before evidence of the neuropathy develops.

Another proposed mechanism involved in OPIDN is an imbalance in calcium homeostasis. It lead to the activation of calcium-activated neutral protease thereby increasing the calcium/calmodulin-dependent protein kinases. It

contribute to aberrant phosphorylation of cytoskeletal proteins and protein digestion in the terminal axon. This results in Wallerian type of degeneration. Experimental studies are still going on in this aspect whether replacing normal homeostasis of calcium can prevent this complication.

CLINICAL FEATURES:

Usually begins with sensory symptoms in the form of tingling, numbness in the distal extremities. First start with lower limb then progresses to upper limb. But sensory neuropathy alone is not the sole manifestation of OPIDN especially in humans.

Later slowly the motor symptoms develop in the form of flaccidity of muscles in the distal extremities. Weakness usually will be bilateral symmetrical. This results in locomotor defects such as high stepping gait. Ataxia has also been reported.

As the disease progresses in severe forms quadriplegia with foot and wrist drop are seen, as well as mild pyramidal signs. (Jokanovic, Stukalov *et al.* 2002) Electrophysiological studies of OPDIP organophosphate suggest features of axonal neuropathy, such as slowing of both motor and sensory conduction. it also have evidence of chronic denervation of distal muscles.

PROGNOSIS:

Usually the recovery happens only in the sensory symptoms. Motor symptoms persist. Sensory symptoms resolve over ensuing 1-2 months.

Patients with mild cases recover over several months; those with more serious polyneuropathies have persistent effects. (van Gemert 1999; Kwong 2002) Functional recovery also depends on the degree of pyramidal involvement and presence of ataxia(, Stukalov *et al.* 2002).

So far No specific treatment has been identified. (Dewhurst 2000)

There are controversies regarding the early administration of pralidoxime and atropine .It has been concluded that it does not seem to prevent the condition. (Tareg *et al.* 2001)

DIAGNOSIS OF ORGANO-PHOSPHORUS POISONING:

1.History of exposure to or consumption of organophosphorus poisoning

2. Symptoms like loose stool , dyspnoea and sweating

3 Signs of poisoning like smell of opc , tachypenea, miosis fasciculation, neck muscle weakness,

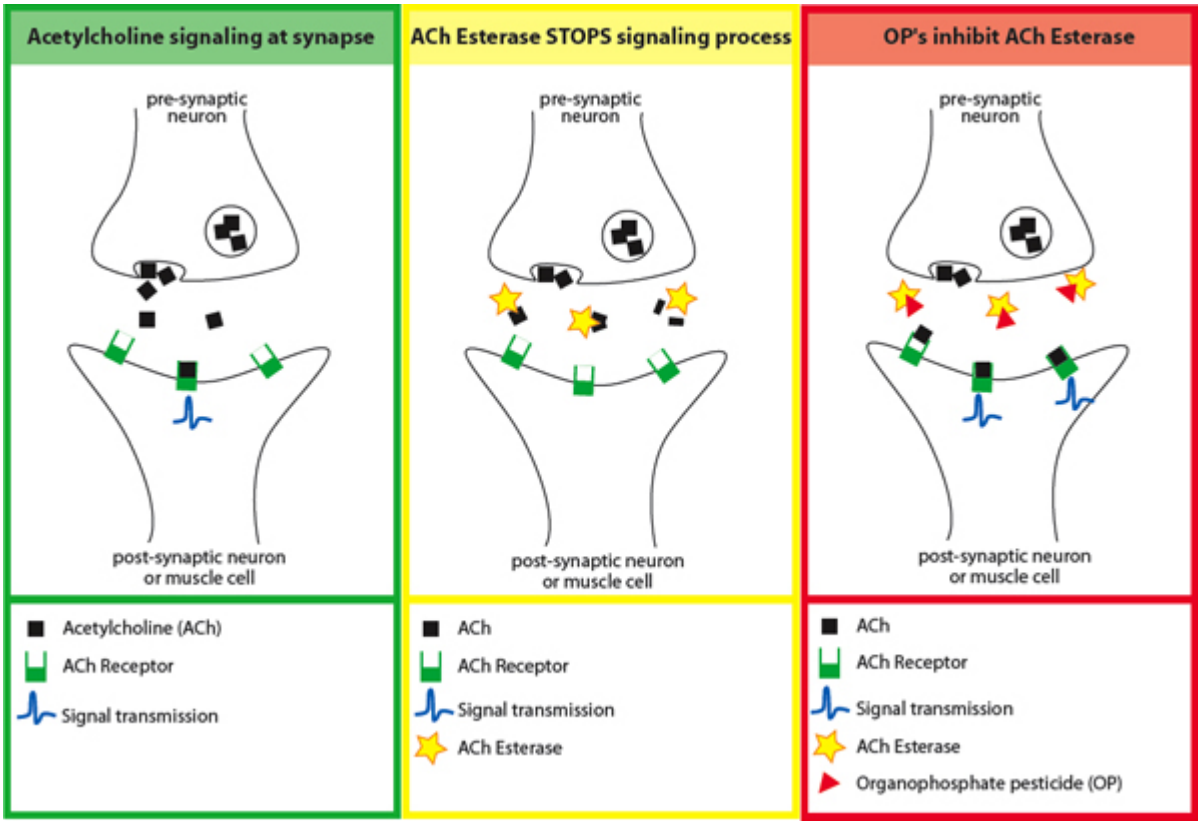
4. Effect of pralidoxime and atropine

5.Inhibition of the cholinesterase activity in the blood

CHOLINESTERASE[40]:

These are the group of enzymes which metabolize acetylcholine in to acetic acid and choline . There are two types of cholinesterase. One is acetylcholinesterase and another is butyrylcholinesterase.

PROPERTIES	ACETYLCHOLINESTERASE	BUTYRYLCHOLINESTERASE
SYNONYM	RBC CHOLINESTERASE	PLASMA /PSEUDO CHOLINESTERASE
SITE	NM JUNCTION RBC SURFACE	PLASMA (PRODUCED BY LIVER)
SUBSTRATE	ACETYL CHOLINE	BUTYRYL CHOLINE
EASE OF AVAILABILITY	LITTLE DIFFICULT (NOT AVAILABLE IN ALL THE CENTRES)	BETTER
ACCURACY	GREATER	COMPARATIVELY LESS
ONSET OF DEPRESSION	LATER	EARLY
DEPRESSION LASTS FOR	DAYS TO WEEKS	EVEN UP TO MONTHS



Even though many methods are available for determining cholinesterase inhibition, the usual method of analysis is based on the method of Gal and Routh (, as performed on the Dupont automated clinical analyzer instrument.

In this method butyrylthiocholine is used as a substrate. It is hydrolyzed by the enzyme plasma cholinesterase to thiocholine. This thiocholine in turn reacts with a colored dye, 2,6-dichlorophenol,later converted to a colorless form.

The total decrease in absorbance is measured.

The Dupont instrument tests the level of cholinesterase present in the blood serum.

The sample should be taken before the administration of drugs such as Pralidoxime since it will alter the levels of cholinesterase in the serum.

Based on the Marshfield methods of testing, reference values have been for the normal population as follows.

In Males: 10.1-22.1 U/ mL (units per milliliter)

In Females: 8.3-20 U/ mL

Clin. Chem. Acta 1957; 2:316)

Grading according to cholinesterase activity[41]:

20-50% of cholinesterase activity –Mild poisoning.

10-20% of cholinesterase activity – Moderate poisoning.

<10% of cholinesterase activity - Severe poisoning.

MANAGEMENT OF ACUTE ORGANOPHOSPHORUS POISONING [42]

OPC poisoning is a medical emergency. They should be admitted in ICU with adequate ventilation. The health care workers should wear personnel protecting equipments. Rubber Gloves and gowns are recommended.OPC poison penetrate latex /vinyl gloves. For respiratory protection charcoal cartridge. masks are recommended

1. SUPPORTIVE MEASURES:

Oral suction of secretions

Maintenance of circulation

Establishment of respiration

2. PREVENTION OF ABSORPTION:

Decontamination

Emesis

Adsorbents

Cathartics

Bowel wash

3. SPECIFIC THERAPY: [43,44,45]

Atropine

Oximes

Treatment of complications

SUPPORTIVE MEASURES:

Upper airway should be cleared of secretion by intermittent suction . If airway compromise present should be intubated. Commonest cause of death is respiratory failure. If patient develops signs of respiratory failure positive pressure ventilation should be given .

a. Decontamination:

Contaminated clothing should be changed, Person should be washed with copious amount of water and soap as opc are hydrolyzed. Skin folds and underside of fingernails and long hairs require special attention . Ocular decontamination is more important with water or normal saline. Repeat wash may be needed in incontinent patients.

b. Emesis:

Emesis should be initiated if the patient is conscious, not convulsing or has intact the gag reflex . If the patient is comatosed, convulsing or has lost the gag reflex gastric lavage should preceded by endotracheal intubation.

c. Adsorbent:

If the patient present within 3 hours of ingestion activated charcoal can be given. It may be useful upto 12 hours after ingestion in case of delayed gastric emptying.

d. Cathartics:

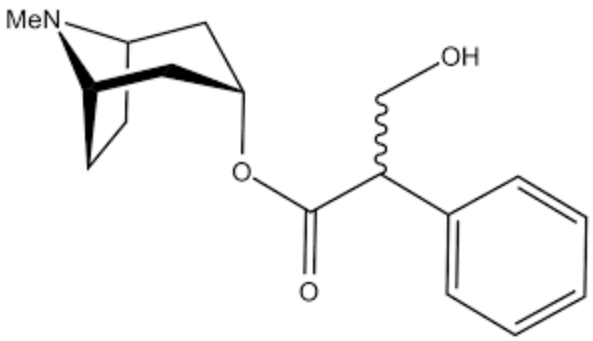
Cathartics decreasing absorption and increasing elimination of poisoning.

e. Bowel wash : It helps to remove the unabsorbed toxic substance from large bowel. It is done twice a day.

SPECIFIC THERAPY:

ATROPINE:

Atropine is physiological antidote for organophosphorus poisoning. It effectively antagonise muscarinic post synaptic membrane receptor mediated effects (bronchial secretion, salivation, increased sweating, bradycardia etc) and in the CNS.



Patient preferably to be oxygenated prior to atropine.

DOSING OF ATROPINE:

There are plenty of literature regarding the dosing schedule of atropine.

Thirty eight different dose schedule has been described. Final concluding thing is have to give a bolus till the needs achieved. Then continuously have a maintenance dose. [46]

The peak effect of atropine is at three minutes. So reassess the patient every min till the signs of atropinization is achieved.

The loading dose atropine should be 1.8-3 mg rapidly IV. Further dose should be repeated at every 5-10 minute according to muscarinic symptoms like bradycardia, miosis, bronchorrea are relieved.

Other routes of atropine delivery includes nebulisation which also helps in improving the oxygenation.

At emergency situations atropine can also be given via endotracheal tube because of its property of absorbing via mucous membrane.

The aim of anti cholinergic treatment is drying of the secretions of tracheobronchial tree and other secretions, and increasing the heart rate. Early response to atropine is pupillary dilatation.

Infusion of atropine at a dose of 0.02-0.08mg/kg/h can also be used.

This therapeutic approach has significant reduction in mortality when compared with intermittent therapy. This should be monitored every 15 minutes.

If atropinization is lost, again give bolus of atropine and the infusion rate should be increased. If there is a evidence of atropine toxicity, atropine infusion should be stopped and treat the toxicity. After settle down of signs of toxicity infusion can be restrated at a rate of 70-80% of previous rate. After reduction of rate of

infusion patient monitored hourly then 2-3 hourly. Infusion of atropine need to be continued for 2-5 days and tapered over 3-7 days.

Atropine should be particularly used in caution in elderly individuals with coronary artery disease in whom tachycardia will precipitate failure.

Tachycardia itself is not a contraindication to atropine treatment (A heart rate>140 should be avoided).

TARGET OF ATROPINE THERAPY:[30]

1. Pulse rate should be more than eighty.

2. SBP maintained more than 90 mm Hg.

3. Lung should be cleared from secretions; no wheeze/crepts

4. Axilla should be dry.

5. Pupil should not be pinpoint.

PHARMACOLOGY OF ATROPINE:

NATURAL SOURCE OF ATROPINE:

It is a plant alkaloid derived from atropa belladona or death shade and in Datura stramonium, sacred Datura or datura or thorn apple.

ABSORPTION:

Well absorbed from the gut and conjunctival membranes even absorbed across the skin.

DISTRIBUTION:

Widely distributed in the body. Atropine also crosses the blood brain barrier and counteracts the effects of acetylcholine accumulation in the CNS.

Significant levels achieved in CSF within 30minutes to 1hour.

METABOLISM AND EXCRETION:

Elimination occur in 2 phases namely fast and slow phase. The t1/2 of rapid phase is 2 hours and slow phase is 13 hours.

About 50% of the drug excreted unchanged in urine. The parasympathetic effect last longer in eye for >72hours.

PHARMACODYANAMICS:

Atropine is reversible blocker of muscarinic receptor. Binding of atropine to muscarinic receptor prevents release of inositol triphosphate (IP3) and inhibition of adenyl cyclase. Salivary, bronchial and sweat glands are highly sensitive to atropine. Parietal cells of stomach is least sensitive. Atropine is highly selective for muscarinic receptor. Atropine has no difference at M1,M2,M3 receptors.

EFFECT ON VARIOUS ORGAN SYSTEM:

CENTRAL NERVOUS SYSTEM:

In usual doses has minimal CNS stimulant effect on medullary parasympathetic centre and long lasting sedative effect on brain.

EYE:

Mydriasis, Cycloplegia, reduce lacrimal secretion. All these effect contributes to the blurred vision following atropinization which may sometimes even last up to one week.

CARDIOVASCULAR SYSTEM:

In Low doses it will cause bradycardia by blocking prejunctional M1 receptor. shorten the PR interval on ECG by blocking muscarinic receptor in A-V node. Moderate dose cause tachycardia by blocking vagal slowing. In toxic doses cause intraventricular conduction disturbances due to local anesthetic action. Atropine block parasympathetic mediated coronary dilation. Blood pressure level is minimally affected by atropine.

RESPIRATORY SYSTEM:

Atropine cause bronchodilation, reduce the bronchial secretion.

GASTROINTESTINAL TRACT:

Reduces the salivary secretion more than gastric secretion. G.I smooth muscle motility decreased from stomach to colon. Gastric emptying delayed, intestinal transit time prolonged.

GENITOURINARY TRACT:

Relaxes the smooth muscle of the ureters and bladder wall and slow voiding .No effect on uterus.

SWEAT GLANDS:

Thermoregulatory sweating is suppressed by atropine. In adults atropine fever is common following a large dose where as in children and infants its common even with small doses.

ATROPINE TOXICITY:

Atropine toxicity manifests as dry mouth, dry flushed hot skin, dilated pupil, excitement, delirium, palpitation, hypotension, cardiovascular collapse, convulsions and coma.

Most of these features are indistinguishable from acute organophosphorus poisoning. This condition should be identified and adequate dose adjustment should be made.

GLYCOPYRROLATE: [47]

Glycopyrolate (0.5mg/kg), a quaternary ammonium compound, may be substituted for atropine, if there is no evidence of central toxicity. It has got many theoretical advantages over atropine for treatment of organophosphorus poisoning. It does not cross the blood brain barrier thus eliminating the potential for central effects. There is also less tachycardia and better control of bronchial secretions and hence lower incidence of respiratory infections.

OXIMES- CHOLINESTERASE REACTIVATORS[48,49,50]**:**

Pralidoxime (2-Hydroxy iminomethyl- 1 –pyridinium chloride, 2-PAM; pyridine 2 aldoxime methyl chloride)

Actions of pralidoxime:

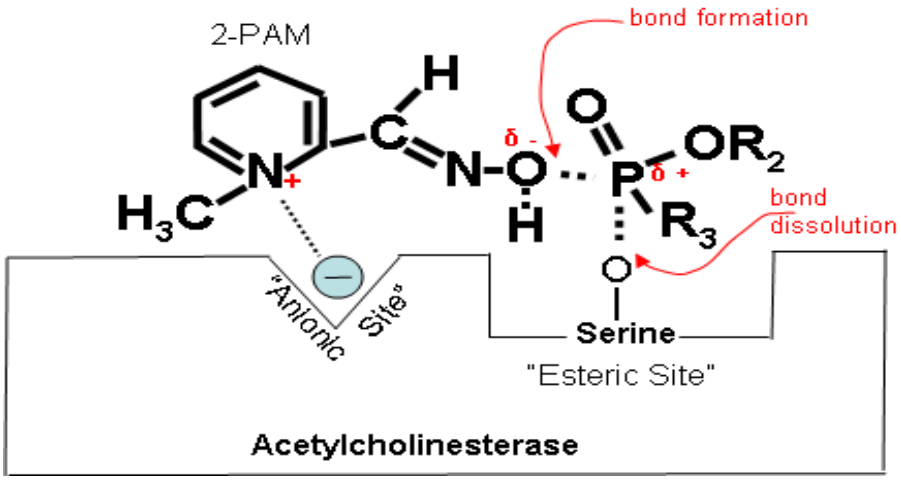
1. Reactivation of cholinesterase by cleavage of phosphorylated active sites
2. A direct reaction and detoxification of unbounded organophosphorus molecules
3. Endogenous anticholinergic effect.

2-PAM binds to the area where the compound has attached to and blocked the enzyme cholinesterase. Then the drug attaches to the inhibitor and take it off from the enzyme cholinesterase, making the enzyme to function normally. This process is referred to as “regeneration” of cholinesterase.

Pralidoxime works by competing for the phosphate moiety of the OP compound

and releasing from the acetyl cholinesterase enzyme.

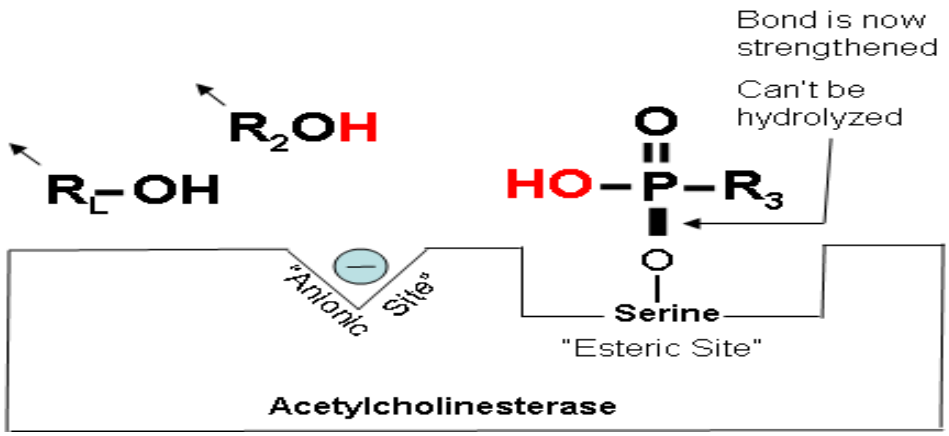
This action only occurs shortly after poisoning and inhibition of enzyme, after which the enzyme “Ages” and becomes irreversibly inactivated.



What is aging ?

After a period of time this inhibitors forms a strong irreversible bond with the enzyme. So oximes cannot bind with the enzyme after this bonding. This particular times varies in respect to each compound. Beyond that time oximes have no

beneficial role.



Some of the examples given by hoffman include soman in which it occurs in 2 minutes, VX it takes 40 hours.

Role in Carbamate poisoning:

Pralidoxime has actually no role in carbamate toxicity because the bond formed between the toxic compound and enzyme lyses on its own within a few hours. The bond usually do not undergo the aging process. Usually the symptoms recover within a few hours.

Although pralidoxime is most effective when administered early, it continues to have salutary effects for a prolonged period of time after exposure. The oximes are probably most effective if given within 6hours of poisoning. Early evidences

suggested that to be successful, cholinesterase reactivators must be administered within 24-48hours of exposure to organophosphates.

There Are Certain Situations In Which Oximes Have To Be Given For Long Time Or It Can Be Started Even After The Period Speculated For Aging. Three Such Situations Are Described In Literature.

1 . Compounds which are soluble in fat will remain there for long time and release after the speculated time which leads to clinical manifestations later due to reinhibition of enzymes.

2. For a op compound to cause clinical features it should form a active metabolite. it will take some time.

3 .Some time skin exposure will cause delayed manifestations.

Pralidoxime is renally excreted and within 12hours 80% of the dose has been recovered unchanged in the urine. The plasma half life is 75minutes.

The adult dose is 1-2g (of pralidoxime chloride) in 100-150mL of 0.9% sodium chloride given intravenously over 30minutes. This dose can be repeated

in hour if muscle weakness and fasciculations are not relieved. This dose should be

repeated at every 6-12hours interval for 24-48hours. This may result in reappearance of toxicity before the next dose because the serum concentration would be expected to fall to less than therapeutic levels within several hours. So a continuous infusion of 500mg/hour has been advocated for severe poisoning.

Maximum dose advised by British national formulary is 12 grams per day.

ADVERSE EFFECTS:

Adverse effects of 2-PAM in humans have been absent or minimal and may not be evident until very high plasma levels (400mg/mL).

1.Transient dizziness, Dry mouth

2. Visual disturbances (transient) secondary to raised intraocular pressure.

3. Elevation of diastolic BP may be related to the rate of infusion.

4. Rapid IV administration even at routine dose of 2gms over 10 min has been documented to produce sudden cardiac arrest.

5. Higher doses can even itself produces neuromuscular blockade.

6. Interacts with atropine and sometimes precipitate atropine toxic effects.

Other oximes: The use of sugar oximes (the molecular combination of glucose with 2-PAM derivatives) to promote CNS penetration appears promising.

OBIDOXIME :

(Toxogonin) contains two active sites per molecule and is more potent than 2-PAM. The H series of oximes (named after Hagedorn) HI-6, HJ-6 have been developed against chemical warfare nerve gases. In addition to reactivating cholinesterase they have direct central and peripheral anticholinergic effects.

It was Eyer F et al., who studied the effect of Obidoxime in organophosphate poisoning in relevance to their clinical features and cholinesterase level. The study revealed that this oxime particularly responds to parathion rather than other OPCs.

PHARMACOKINETICS:

Elimination half life : 6.9 h

Vd: 0.845 L/kg

Renal clearance : 69 mL/min

Obidoxime dose must be titrated according to renal function. Further randomized controlled trials are must to determine the therapeutic window of this compound with organophosphate intoxication.

Jokanović M et al.,[51,52]conducted a trial of comparison between 3 oximes and HI6 in OP compound poisoning in rats. The study provens that even oximes is the effective antidote in phosphonate compounds. It concluded that Trimedoxime was the most effective drug in treatment of OP poisoning in rats. No such trials are available in humans.

MANAGEMENT OF COMPLICATIONS OF ORGANOPHOSPHORUS POISONING:

a. Seizures: Benzodiazepine.

Diazepam IV (Child: 0.2 to 0.5 mg/kg, repeated every 5 minutes as needed Adult: 5 to 10 mg, Q 10 to 15 minutes as needed).

If seizures recur, phenobarbital 10 mg (children > 5 years) or 30 mg (adults).

b. Hypotension : IVfluids

Place in trendelenburg position.

Infuse 10 to 20 mL/kg isotonic fluid.

If hypotension persists, administer norepinephrine (0.1 to 0.2 mcg/kg/min) or dopamine (2.5 to 20 mcg/kg/min) and titrate accordingly.

c. Pulmonary Edema (Noncardiogenic) :

Maintain ventilation and oxygenation and evaluate with frequent ABG or pulse oximetry monitoring. Early use of PEEP and mechanical ventilation may be needed.

d. Eye Exposure :

Repeated washing of eyes with cold water.

Drugs contraindicated in organophosphorous poisoning :

1. Succinylcholine.

2. Phenothiazines.

3. Antihistamines.

4. Opiates.

5. Barbiturates.

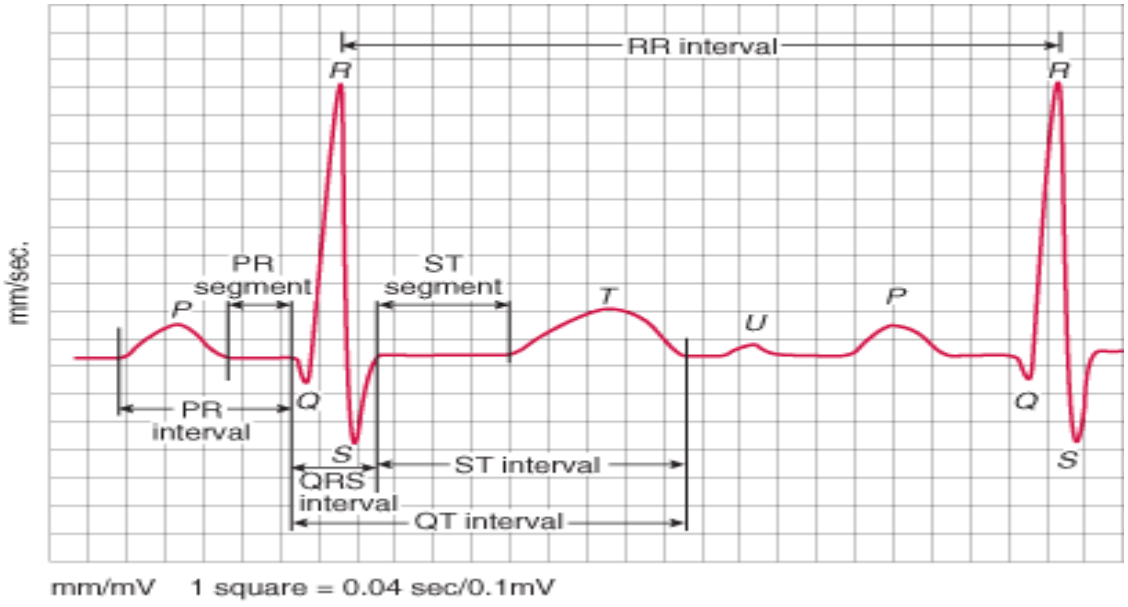
6. Epinephrine.

7. Aminophylline.

QTc INTERVAL

QT interval in ECG indicates the time taken for the ventricle depolarization and repolarization.

It is calculated from start of Q wave up to end of T wave.

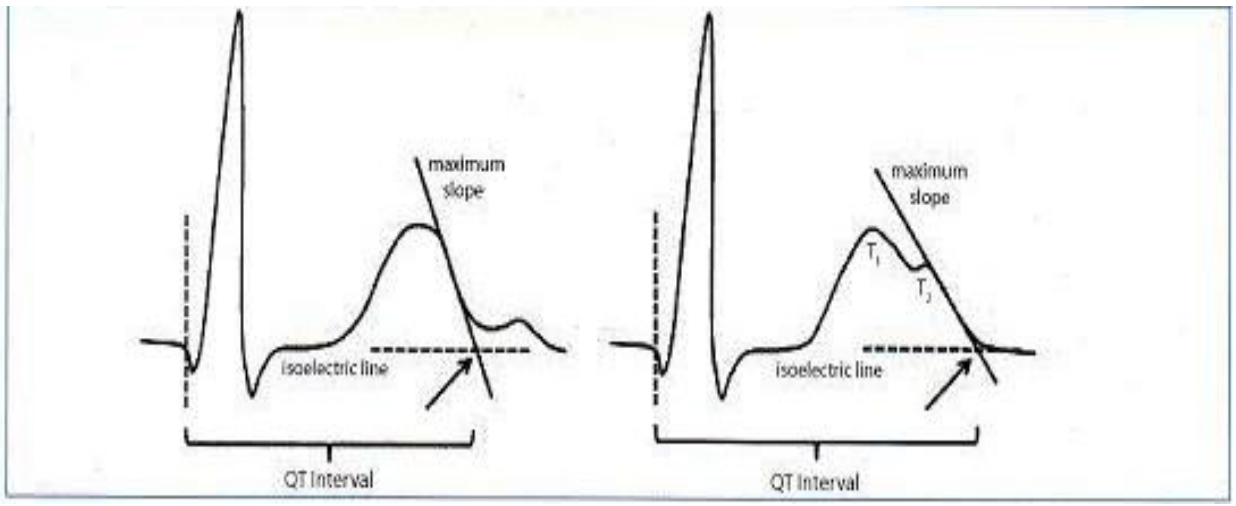


Ideally it should be measured in lead 2 or in V5 -6.

It should be measured in two successive leads. The maximum with in the two should be taken.

There is always a confusion in measuring QT interval. Because of the presence of U wave ,which makes to differentiate the end part of T wave.

To avoid that slope intercept method is used.



In this method the T wave end is defined as the intercept line which is tangential line drawn across maximum slope of T wave.

When there are notches in the T wave as in the second graph ,,the tangent line is drawn from maximum slope down to second part of the notch T2 .

Whenever the U wave is large and when it is found to be fused it should e incccluded in the measurement. large wave is defined as U wave more than 1mm.

Some literature mentioned that the tip of the notch should be considered as the end of T wave for all practical purposes.

When U wave is separate or small it can e excluded from the QT interval measurement.

QT interval varies significantly with heart rate. since it is the representation of the action potential of the myocardium, which in turn depends on the rate. It is the rate which estimates the repolarisation time.

The QT interval won't change instantly in response to the rate. It will take 1 to 3 minutes for full adaptation. This too varies individually.

It is not fixed to have same change in QT interval in response to rate. It also depends on the associated sympathetic discharge for example the hanges will e less during the cold pressor test.

But it is not the rate alone which determines the QT interval it is influenced by numerous other process which will be discussed below.

It may be physiological , pathological or most importantly pharmacological.

PHYSIOLOGICAL VARIATIONS IN QT INTERVAL:

The normal variability is accounted to some unknown genetic factors.

QT interval increases with age .

Females normally have increased QT in comparison with males.

QT interval decreases by 20 milliseconds in men after puberty ,but this is not found in case of females.

As with any other metabolic changes in our body QT interval also changes in respect to circadian rhythm. The reason is not known for the prolonged QT interval during the night.

PATHOLOGICAL VARIATIONS IN QT INTERVAL:

Congenital long QT interval due to channelopathies (mostly genetic).

Alcoholic with histological evidence of cirrhosis shows prolonged QT interval in most of the studies.

Prolonged QT interval will be also seen in anorexia nervosa.

Exercise increases the heart rate which in turn influence the QT interval. A study has been done in this influence of rate in exercise to change in QT interval.they concluded that two third of the changes can be attributed to the rate ,remaining due to various autonomic changes related to catecholamine secretion.

Corrected QT interval[53] :

Since 1920 there are dozens of formula to correct QT interval. But almost every thing involves the correction with respect to rate. All having its own limitations . Most commonly used is Bazzets formula.

The initial formula formulated by him was QT= k * square root of RR

Fridericia proposed a cube-root formula:

QT= k *cube root of RR

Where k value is 0.37 in men and 0.40 in women which was measured to a QT interval measured at a heart rate of 60 beats per minute.

At present, Bazett's formula is used in the following form:

$$QTc = \frac{QT}{\sqrt{RR}}$$

It is expressed in terms of seconds.

The major limitation of bazett formula is that When heart rate is particularly fast or slow, this formula may overcorrect or undercorrect, respectively.

The cube root Fridericia formula has the same limitations as said above but at limited to only slow heart rates.This formula is considered as a more accurate correction factor in individuals with tachycardia.

There is no clear guideline to say what is the best formula to be utilized in clinical practice.**54**

In normal situations with heart rates of 60-90 beats/min range, almost all the formulae give similar results for the diagnosis of QT prolongation.

It was Ashman who first proposed the logarithmic formula which defines

$$QT = K1 \times \log(10 \times [RR + K2])$$

where K2 = 0.07; K1 = 0.380 for males & 0.390 for females.

But in low heart rates, the results given by this formula are too low.

Adams proposed the first linear formula has been

for women: $QT = 0.1259 \times RR + 0.2789$

for men: $QT = 0.1536 \times RR + 0.2462$

Schlamowitz proposed the following formula for the general population:

$$QT = 0.205 \times RR + 0.167$$

Even if the rate dependence of the QT interval is probably best described by an exponential relation, in the normal heart rate range the QT-RR relation is approximately linear.

In young adults during sleep there will be a increase in heart rate so Bazett , Hodges formula tends to overestimate the correction where as Framingham & fredrichia underestimate the correction. But its found that Hodges is better during sleep.

Various formulas has been described

But nothing has been proved one is superior to other.

Bazett modified by Taran and Szilagyi	**QTc = QT / (RR)½**
Fridericia	**QTc = QT / (RR)(0,33)**
Framingham	**QTc = QT + 0,154 (1−RR)**
Lecocq	**QTc = QT/RR(0.314)**
Malik	**QTc = QT/RR x 0,371**
Sagie	**QTc = QT + 0.154 (1 – RR)**
Boudolas	**QTc = QT + 2,0 (FC – 60)**
Schlamowitz	**QTc = QT + 0,205 (1 – RR)**
Wohlfart	**QTc = QT + 1,23 (FC – 60)**
Larsen and Skulason	**QTc = QT + 0,125 (1 – RR)**
Mayeda	**QTc = QT/RR x 0,604**
Kawataki	**QTc = QT/RR(0,25)**
Van de Water	**QTc = QT – 0,087 (RR – 1000)**
Matsunaga	**QTc = log (600) QT / (log RR)**
Sarma	**QTc = QT - B1 Exp (-k1 . RR)** **QTc = QT [1-Exp (-k2 . RR)]** **QTc = QT (RR)½ + B3** **QTc = QT (RR)½ ***
Hodges	**QTc = QT + 1,75 (FC − 60)**
Strength equation	**QTc = 453,65 × RR1/3.02 (R2 = 0,41)**

B and k: are regression parameters.

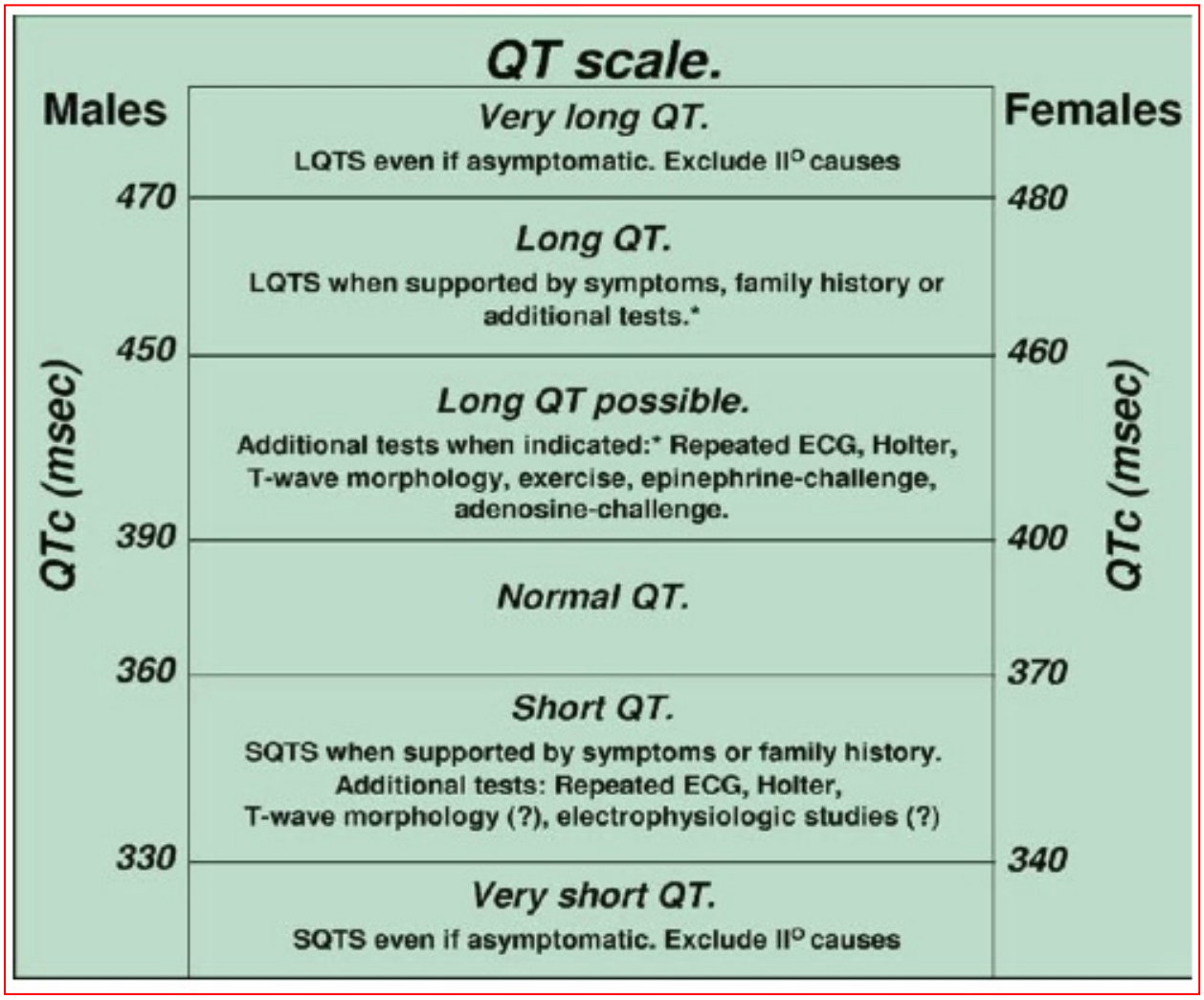
Exp: exponential function with base e = 2,718.

FC: heart rate.

RR: RR distance.

*** It is stated that this formula is better than Bazett's**

NORMAL QT INTERVAL:



WHY QT INTERVAL IS PROLONGED IN OP POISONING ?

The exact pathophysiology of cardiac manifestations and electrocardiogram changes remains unknown.

The common ECG manifestations includes sinus bradycardia, sinus tachycardia, prolonged PR interval ,prolonged QTc interval ,VPCs,ventricular tachycardia ,torsades de pointes.

Prevalence varies in different studies conducted at various places.

It was ludomirsky et al., [55] who proposed three different phases involved in cardiotoxicity of OPC poisoning.

Phase 1:

Increased sympathetic activity which is very transient which is followed by

Phase2:

Increased parasympathetic activity

Phase 3:

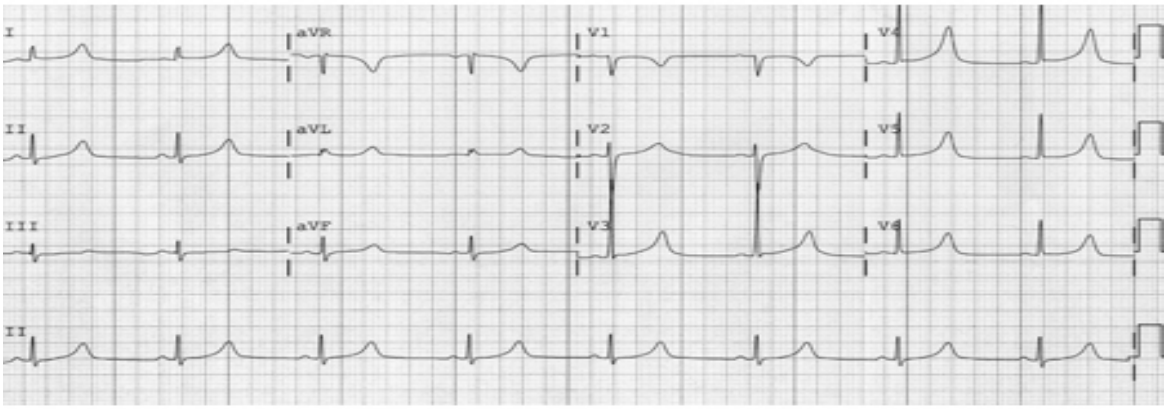
QTc slowly starts increasing then when severe may lead to TDP ultimately ventricular tachycardia.

This is because of this changing phases some presents with tachycardia some with bradycardia.

Not all patients with prolonged QTc are at risk of having ventricular tachycardia(67%)

This is the ECG of one of our patients who show sinus bradycardia with prolonged QTc.

Other examples are attached at the end.



MATERIALS AND METHODOLOGY

PLACE OF STUDY:

This study was conducted at the Department of Internal Medicine at Thanjavur Medical college hospital during JANUARY 2014- AUGUST 2014.

TOTAL NUMBER OF PATIENTS INCLUDED IN THE STUDY :

70 patients (including both males & females).

GEOGRAPHIC DISTRIBUTION:

Patients included in this study were from Urban & Rural areas of Ariyalur, Perambalur , Thanjavur, Thiruvarur and Pudhukottai districts. As already discussed in the introduction this is a place where this OP compounds are handled in large amounts so it is a suitable place to conduct a study.

INCLUSION CRITERIA:

Patient with history of OPC POISON consumption.

(those who brought the container showing the chemical name of the compound. Oral evidence are not taken in to account)

EXCLUSION CRITERIA:

1.Those not given consent for the study.

2. Unknown poisoning even with clinical features suggestive of OPC.

3. Patients treated outside with atropine.

4. Known coronary artery disease patients.

5. H/O arrhythmias in the past / those who are on Anti arrhythmic agent.

6. Those who taking drugs prolonging QT interval.

PROCEDURE:

Patients admitted in casualty with history of OPC consumption satisfying the above inclusion and exclusion criteria are selected.

After obtaining informed consent from the patient's relative, the patient was evaluated in detail based on history of presenting illness.

Detailed clinical examination done as per the protocol and recorded in the proforma.

The following investigation are done in all patients admitted with OPC compound poisoning.

1. RBS-Random blood sugar
2. Sr. UREA /CREATININE
3. Sr.SODIUM & POTTASIUM

4. **ELECTROCARDIOGRAM 12 LEADS:**

12 LEAD ECG IS TAKEN IMMEDIATELY AFTER ADMISSION BEFORE ATROPINISATION.

THEN THE FOLLOWING PARAMETERS ARE ASSESED IN THE ECG.

1. RATE
2. RHYTHM
3. PR INTERVAL
4. QT INTERVAL
5. QTc by BAZZETs FORMULA
6. ST T CHANGES
7. ANY VPCs.

The patient was followed up till their discharge/death. Their course of stay in the hospital was noted.

Outcome was compared with QTc interval Statistical analysis was made using SPSS software.

Ethical committee clearance has been obtained for all the above said procedures.

RESULTS:

TABLE 1: SEX DISTRIBUTION

SEX	No.of respondents (n=70)	Percentage (100%)
Male	60	85.7
Female	10	14.3

TOTAL NUMBER OF PATIENTS INCLUDED IN THE STUDY WAS 70.

AMONG THEM NUMBER OF MALES WERE 60 i.e) 85.7 %

AMONG THEM NUMBER OF FEMALES WERE 10 i.e) 14.3%

GIVEN BELOW IS THE GRAPHICAL REPRESENTATION OF THE SEX DISTRIBUTION

GRAPH 1:

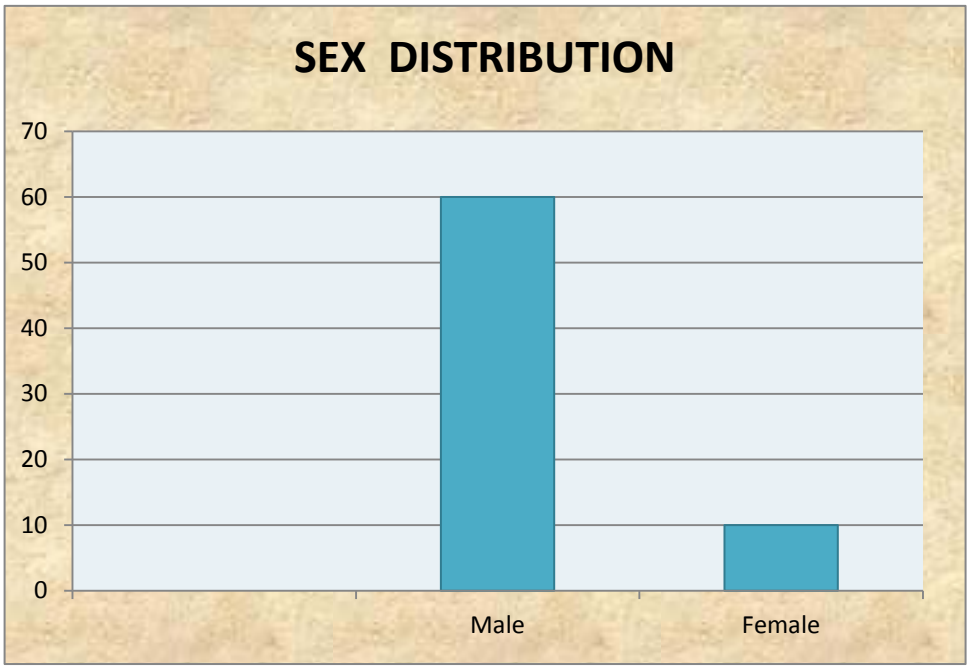


TABLE 2: TIME FOR HOSPITALIZATION

TIME TO ARRIVE	No.of respondents (n=70)	Percentage (100%)
Below 4hrs	26	37.1
4 to 12hrs	44	62.9

THE PATIENTS ARE CLASSIFIED IN TO TWO GROUPS BASED ON THE TIME OF ARRIVAL TO HOSPITAL.

37% OF THEM REACHED WITH IN 4 HOURS.

63% OF THEM REACHED AFTER 4 HOURS.

SHOWN BELOW IS THE GRAPHICAL REPRESENTATION OF THE TWO GROUPS.

GRAPH 2:

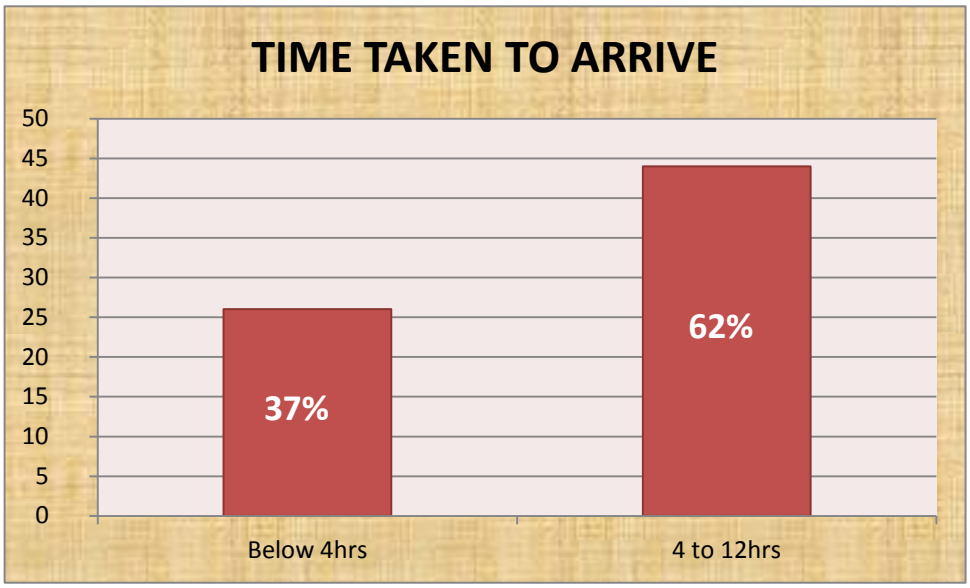


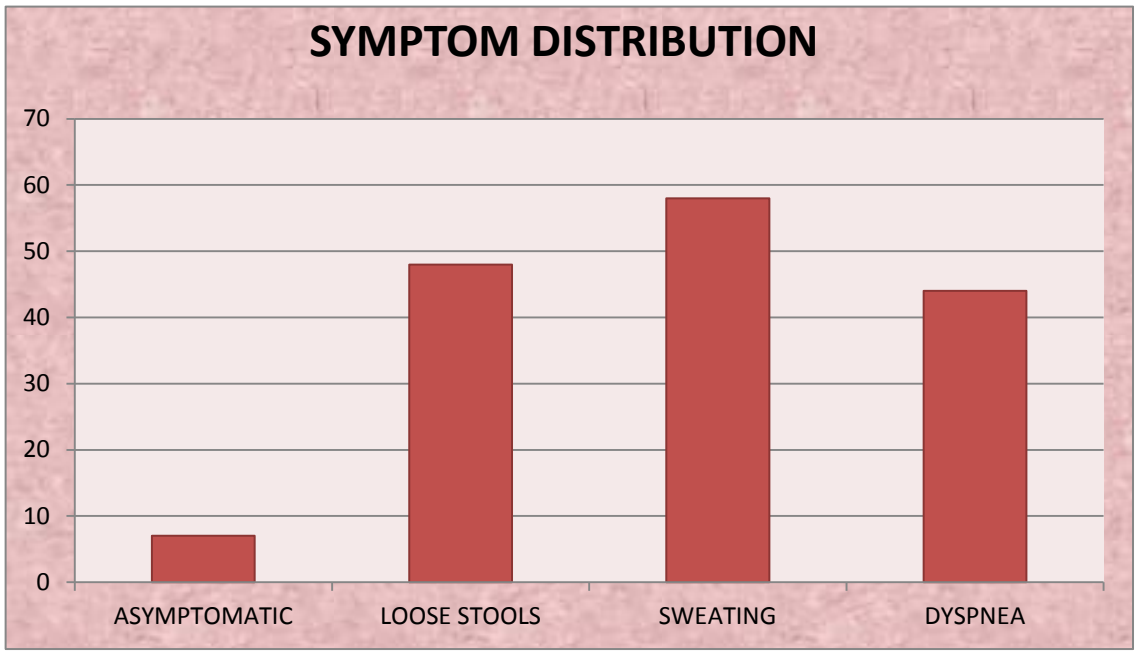
TABLE 3: SYMPTOM DISTRIBUTION

THIS TABLE SHOWS THE SYMPTOMATOLOGY OF THE PATIENTS.

SYMPTOMS	NO OF RESPONDENTS (n=70)	PERCENTAGE
ASYMPTOMATIC	7	10.0
LOOSE STOOLS	48	68.6
SWEATING	58	82.9
DYSPNEA	44	62.9

GRAPH 3:

THIS GRAPH SHOWS THE SYMPTOM DISTRIBUTION OF PATIENTS IN OUR STUDY.



10 % PRESENT WITHOUT ANY SYMPTOMS.

MOST OF THEM PRESENT WITH SWEATING (82.9%) , FOLLOWED BY LOOSE STOOLS (68.6%) , THEN DYSPNEA IN 62.9 % OF INDIVIDUALS.

TABLE 4: DISTRIBUTION OF VARIOUS COMPOUNDS TAKEN

NAME OF THE COMPOUND	NO OF PATIENTS TAKEN N=70	PERCENTAGE (100%)
CHLORPYRIPHOS	19	27.2
MONCHROTOPHOS	22	31.4
METHYLPARATHION	16	22.8
DIMETHOATE	8	11.4
QUINOPHOS	5	7.1

MOST COMMON COMPOUND ENCOUNTERED IN OUR STUDY IS MONCHROTOPHOS (31.4%) FOLLOWED BY CHLORPYRIPHOS (27.2%), METHYLPARATHION (22.8 %) METHYLPARATHION (11.4%) FINALLY QUINOPHOS (7.1%).

GRAPH 4:

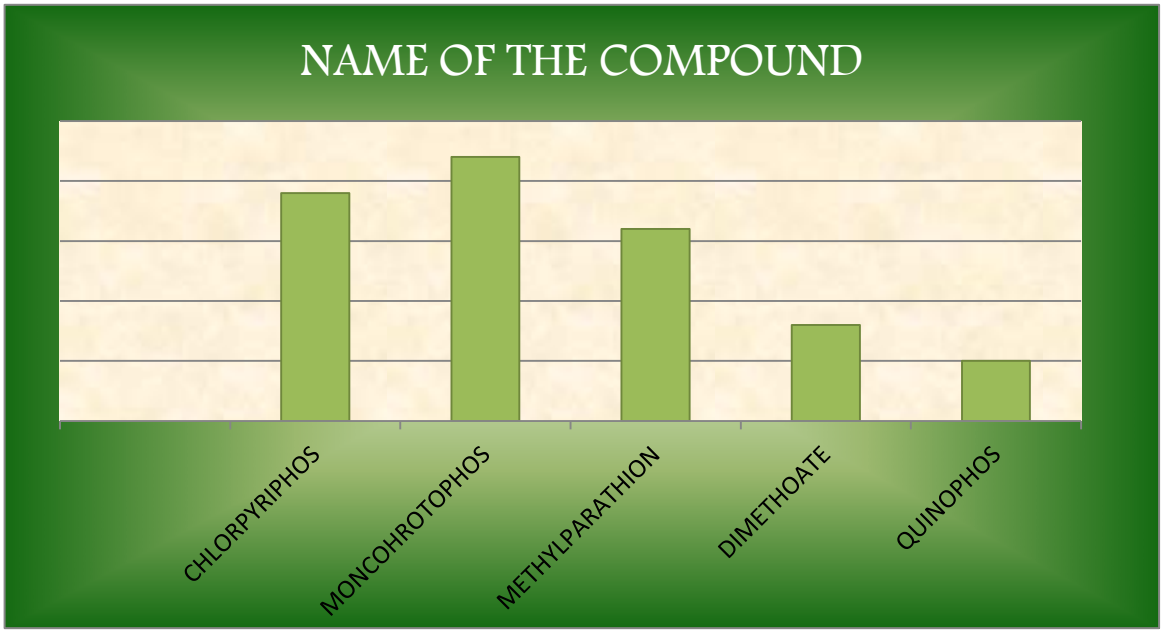


TABLE 5: DISTRIBUTION OF PULSE RATE

PULSE RATE/MIN	NO OF RESPONDENTS (N=70)	PERCENTAGE
<60	25	35.7 %
60-100	40	57.1 %
>100	5	7.1 %

ALMOST 57 % PATIENTS PRESENTED WITH NORMAL PULSE.

35.7 % PRESENTED WITH BRADYCARDIA.

ONLY 7.1 % PRESENTED WITH TACHYCARDIA.

GRAPH 5:

THIS PICTURE IS THE GRAPHICAL REPRESENTATION OF ABOVE CLINICAL DATA.

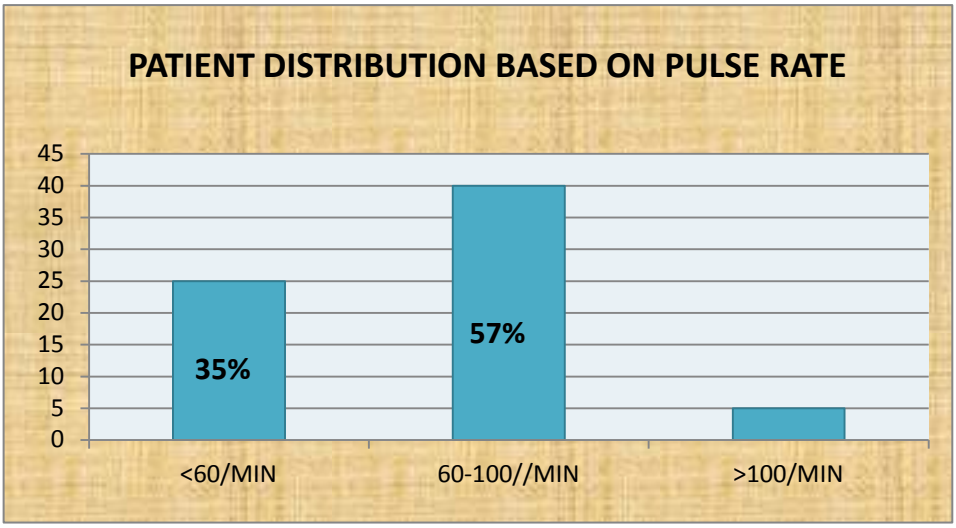


TABLE 6: DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE

SYSTOLIC BLOOD PRESSURE (MM HG)	No. of respondents (n=70)	Percentage (100%)
Below 90 MM HG	23	32.9
90 to 120 MM HG	41	58.6
Above 120 MM HG	6	8.6

MOST OF THE PATIENT (58.6 %) SYSTOLIC BP IS WITH IN THE LEVEL OF 90 –120 MM HG.

ONLY 8.6 % PRESENT WITH SBP >120 MM HG.

GRAPH 6:

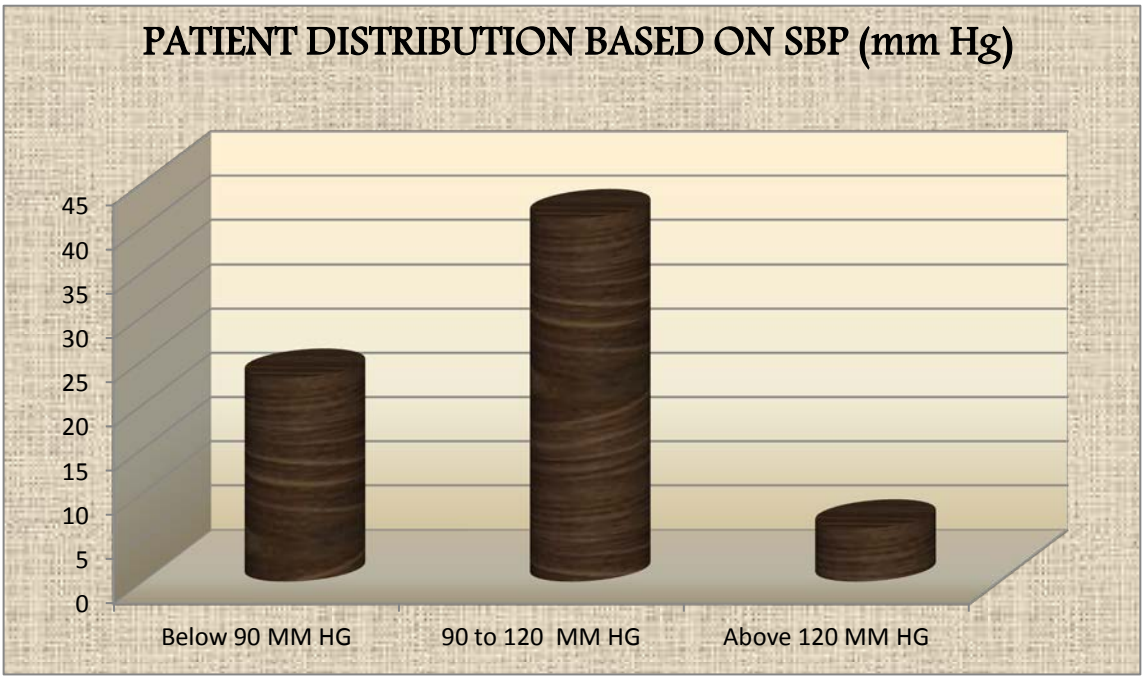


TABLE 7: DISTRIBUTION OF RESPIRATORY RATE

RESPIRATORY RATE PER MIN	NO.OF RESPONDENTS (N=70)	PERCENTAGE (100%)
< 20	46	65%
>20	24	35%

MOST OF THEM HAD RESPIRATORY RATE LESS THAN 20 (65%).

35% HAD RESPIRATORY RATE > 20.

GRAPH 7:

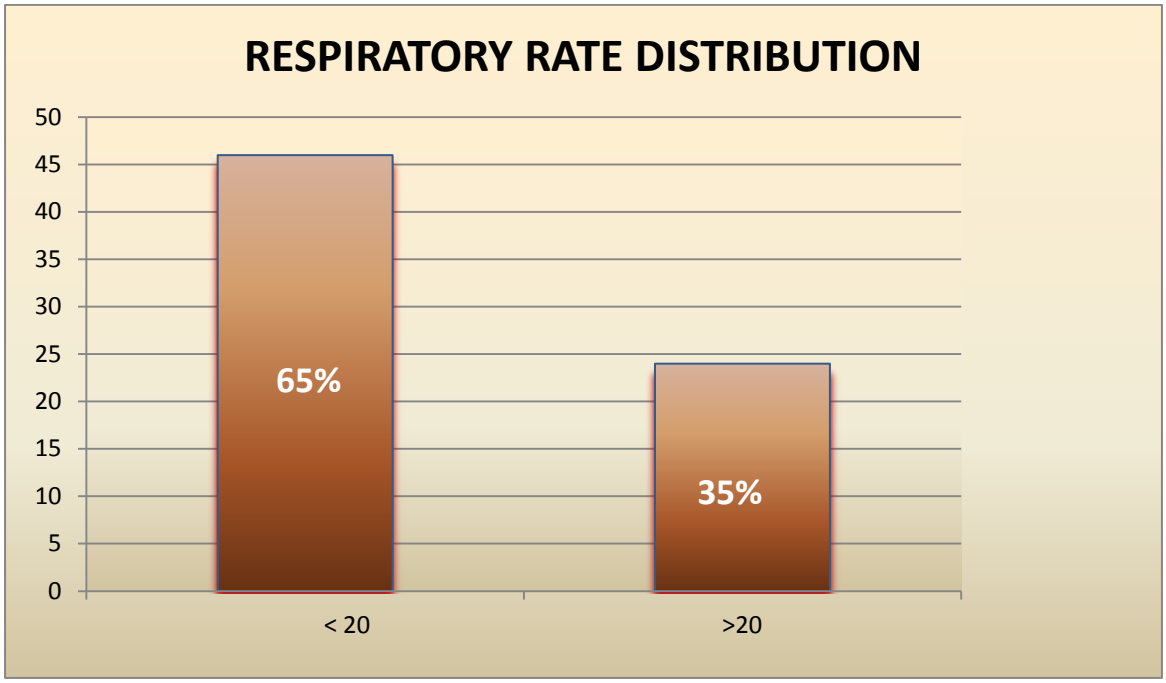


TABLE 8: DISTRIBUTION OF PUPIL SIZE

PUPIL SIZE IN mm	NO.OF RESPONDENTS (N=70)	PERCENTAGE (100%)
1	11	15.7
2	26	37.1
3	31	44.3
4	2	2.9

MORE THAN 50% PRESENTED WITH PUPIL SIZE LESS THAN 2 MM.

47.2 % PRESENTED WITH PUPILS > 2 MM

NO INEQUALITY WAS NOTED IN THE SHAPE OF THE PUPIL.

NO ABNORMALITY IN REACTION TO LIGHT.

GRAPH 8:

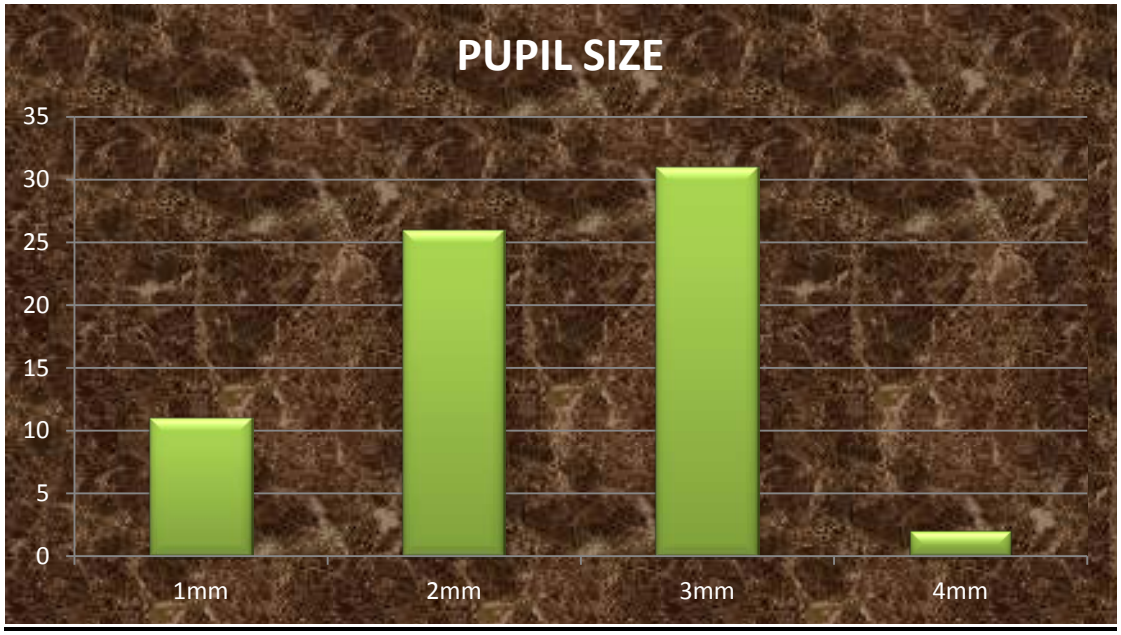


TABLE 9: DISTRIBUTION OF SERUM SODIUM

Sodium levels (mEq/L)	No.of respondents (n=70)	Percentage (100%)
Below 135 **mEq /L**	13	18.6
135 to 145 **mEq /L**	43	61.4
Above 145 **mEq /L**	14	20.0

AROUND 61.4% HAD NORMAL SODIUM LEVELS

ONLY 20% HAD SODIUM LEVELS MORE THAN 145 mEqL

BELOW IS GRAPHICAL REPRESENTATION OF THE SAME DEPICTED ABOVE.

GRAPH 9

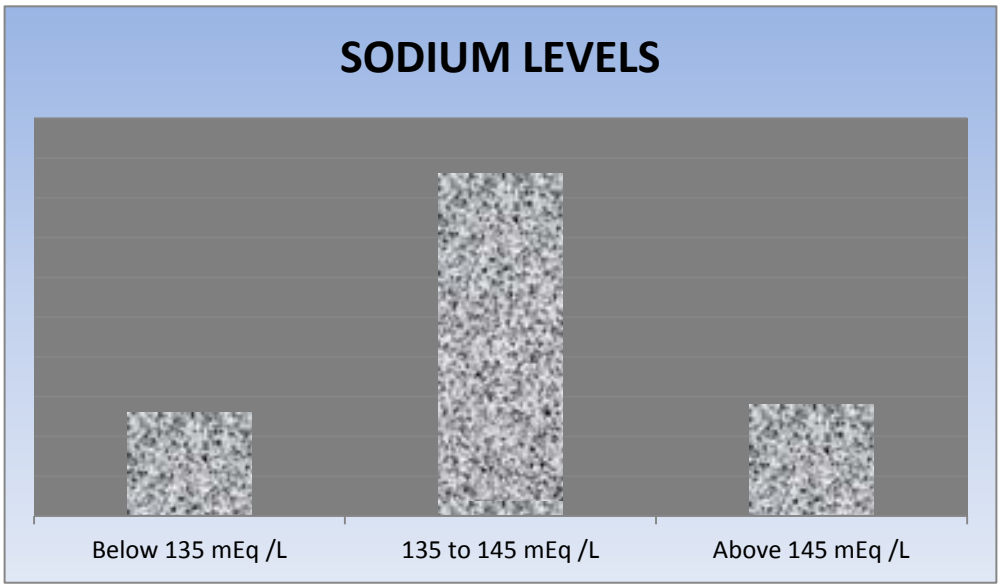


TABLE 10: DISTRIBUTION OF SERUM POTTASIUM

POTTASIUM LEVEL (mEq/L)	NO.OF RESPONDENTS (N=70)	PERCENTAGE (100%)
BELOW 3.5 mEq/L	10	14.3
ABOVE 3.5 -5.0 mEq/L	60	85.7

60 PATIENTS HAVE NORMAL POTTASIUM VALUE.

10 PATIENTS HAVE HYPOKALEMIA**.**

GRAPH 10:

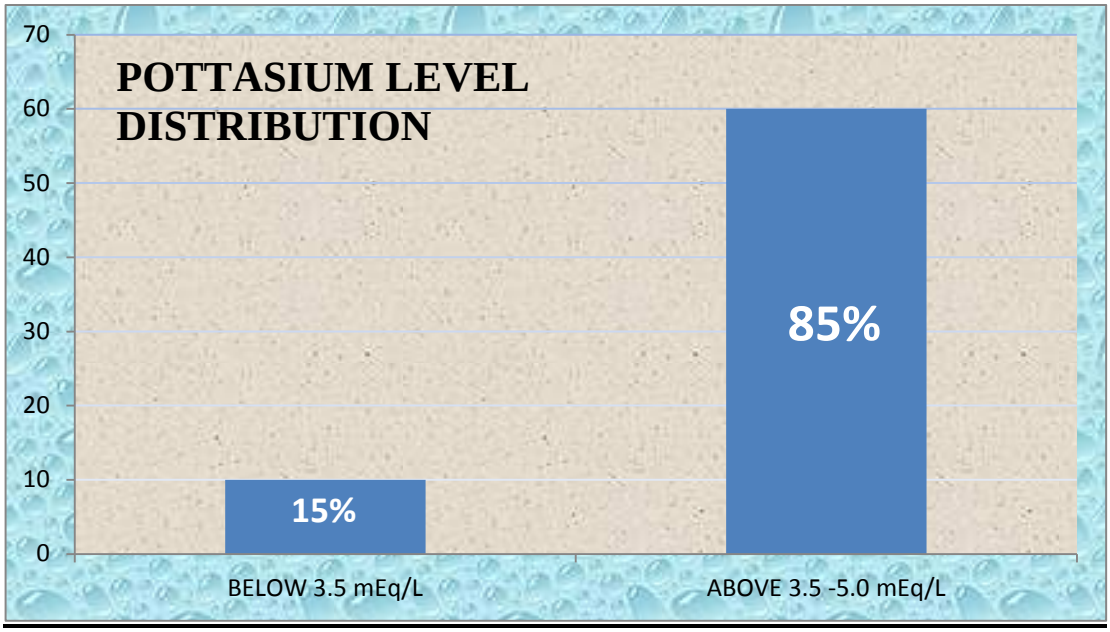


TABLE 11: NEED OF VENTILATOR

PATIENT REQUIREMENT OF VENTILATOR	NO.OF RESPONDENTS (N=70)	**PERCENTAGE (100%)**
YES	18	25.7
NO	52	74.3

ABOUT 25 % PATIENT NEEDS VENTILATOR AMONG THE 70 PATIENTS.

BELOW IS THE GRAPHICAL REPRESENTATION OF THE VENTILATOR NEED IN PATIENTS.

GRAPH 11:

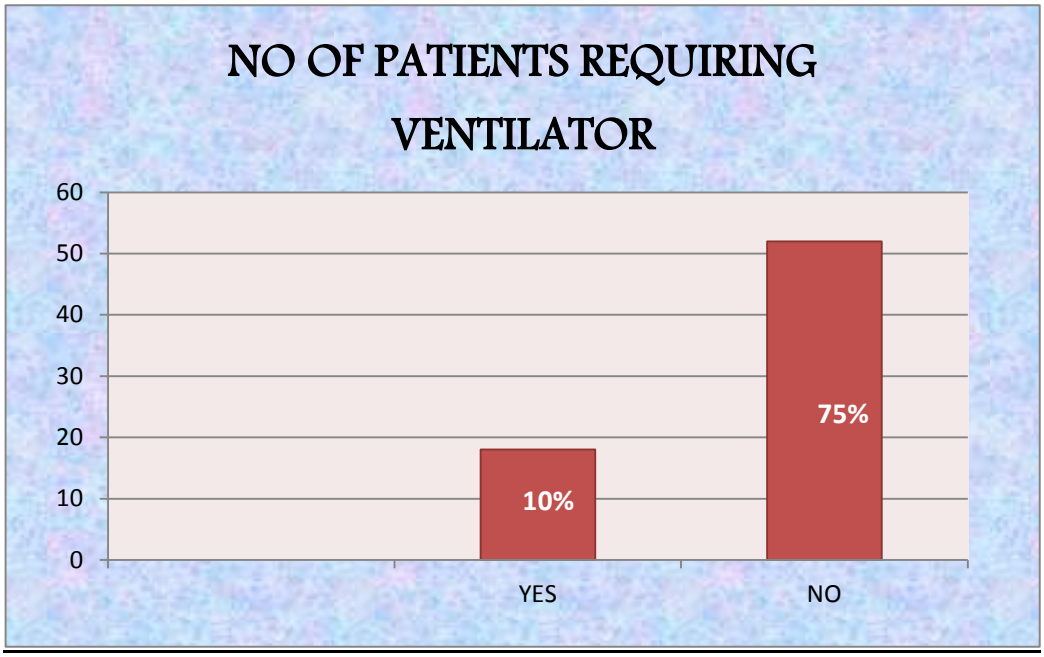


TABLE 12: MORTALITY RATE IN OUR STUDY

OUTCOME	NO.OF RESPONDENTS (N=70)	PERCENTAGE (100%)
DEATH	12	17.1
ALIVE	58	82.9

OUT OF 70 PATIENTS, 12 PATIENTS DIED.

MORTALITY RATE IN THE STUDY IS 17.1 %

GRAPH 12:

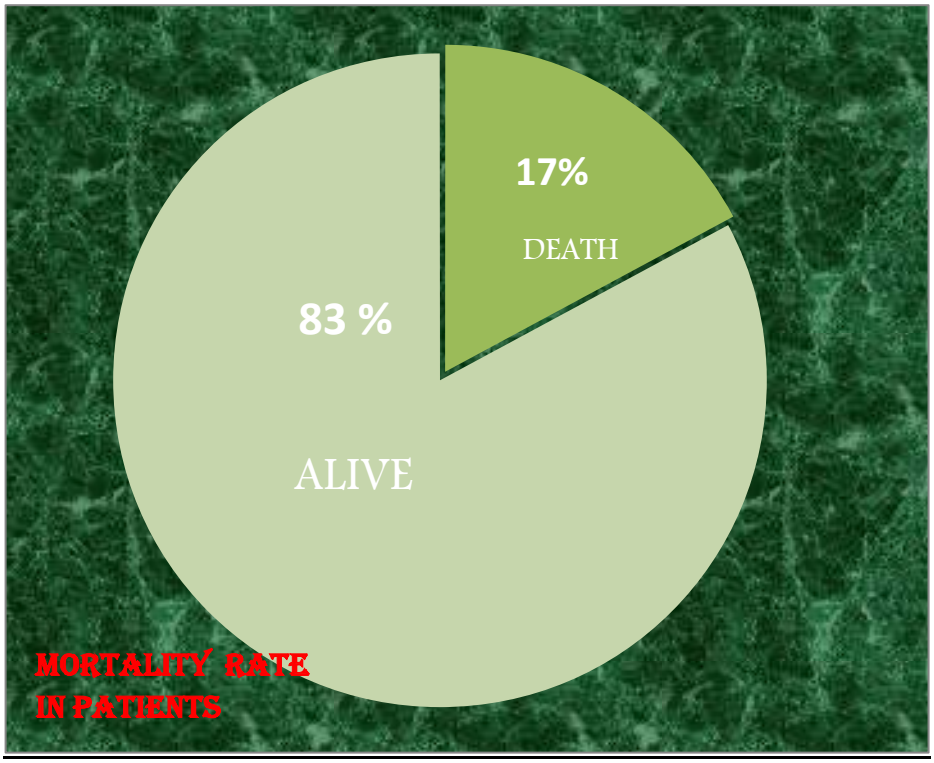


TABLE 13:DESCRIPTIVE STATISTICS OF THE STUDY POPULATION

ITEM	MIN.	MAX.	MEAN	S.D
TIME TO ARRIVE	2	12	5.57	2.476
PR / MIN	44	100	67.07	11.808
SBP MMHG	68	136	100.74	14.019
RR / MIN	8	32	13.37	3.253
PUPIL SIZE (MM)	1	4	2.34	.778
NA 2+	128	154	140.14	5.876
K+	2.70	5.40	4.0057	.51972
RATE IN ECG	50	102	69.59	11.876

THE MAXIMUM AND MINIMUM VALUES IN EACH GROUP ALONG WITH THEIR MEAN AND STANDARD DEVIATION IS GIVEN IN THE ABOVE TABLE.

THESE VALUES WILL BE USED FOR FURTHER ANALYSIS OF THE RESULTS

ANALYSIS OF RESULTS:

TABLE 14:

THIS TABLE COMPARES THE OUTCOME OF THE PATIENT WIHH THAT OF THE SEX OF THE INDIVIDUAL .

SEX	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
MALE	10(83.3%)	50(86.2%)	60(85.7%)	X^2=.067 DF=1 .796>0.05 NOT SIGNIFICANT
FEMALE	2(16.7%)	8(13.8%)	10(14.3%)	

BY CHI SQUARE TEST THERE IS NO ASSOCIATION BETWEEN THE SEX OF THE INDIVIDUAL AND OUTCOME.

SO SEX PLAY NO ROLE IN PREDICTING THE OUTCOME.

BUT THE LIMITATION IN THIS STUDY IS THERE IS A GREAT DISPROPORTION IN NUMBER OF MALE AND FEMALE CASES.

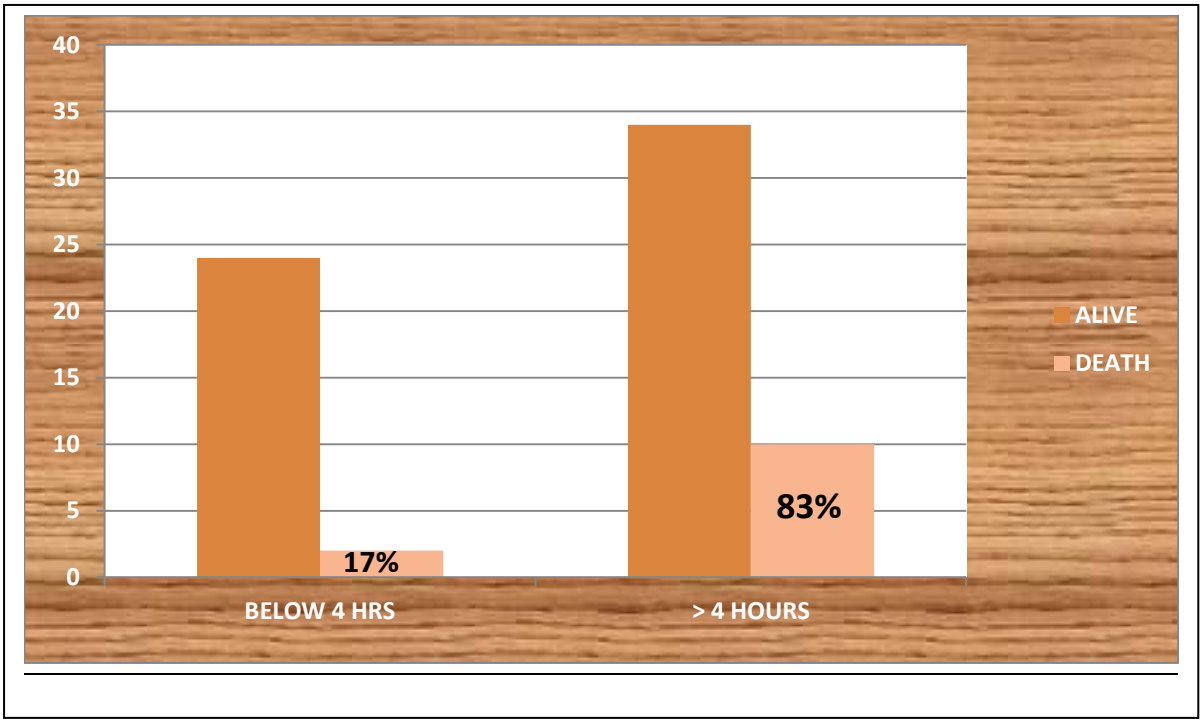
LARGE SCALE STUDIES ARE NEEDED TO CONFIRM THE ABOVE SAID FACT.

TABLE 15: COMPARISON OF OUTCOME WITH RESPECT TO THE TIME OF ARRIVAL

TIME TO ARRIVE	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
BELOW 4HRS	2(16.7%)	24(41.4%)	26(37.1%)	X^2=2.601 DF=1 .107>0.05 SIGNIFICANT
4 TO 12HRS	10(83.3%)	34(58.6%)	44(62.9%)	

The outcome of patients who have arrived more than 4 hours were compared with those who present before 4 hours. There is a change in mortality rate with respect to time of arrival to the hospital.

It is proven statistically by chi square test. SO ACCORDING TO OUR STUDY TIME OF ARRIVAL PLAYS A IMPORTANT ROLE IN PREDICTING THE MORTALITY.



MORTALITY IS VERY HIGH IN PATIENTS ARRIVED AFTER 4 HOURS.

AMONG THE TOTAL DEATH IT OCCUPIES AROUND 83% ,

TABLE 16: COMPARISON OF OUTCOME WITH PULSE RATE

PR / MIN	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
<60 / MIN	10(83.3%)	15(25.9%)	25(35.7%)	X^2=14.304 DF=1 .000<0.05 SIGNIFICANT
60 TO 100 / MIN	1(8.3%)	39(67.2%)	40(57.1%)	
>100 / MIN	1(8.3%)	4(6.8%)	5(7.1%)	

THIS TABLE AND CHARTS DESCRIBES THE DEATH IS MORE IN THOSE WHO PRESENTS WITH BRADYCARDIA WHEN COMPARED TO OTHER GROUPS.

PULSE RATE HAS A STATISTICALLY SIGNIFICANT ASSOCCIATION WITH MORTALITY.

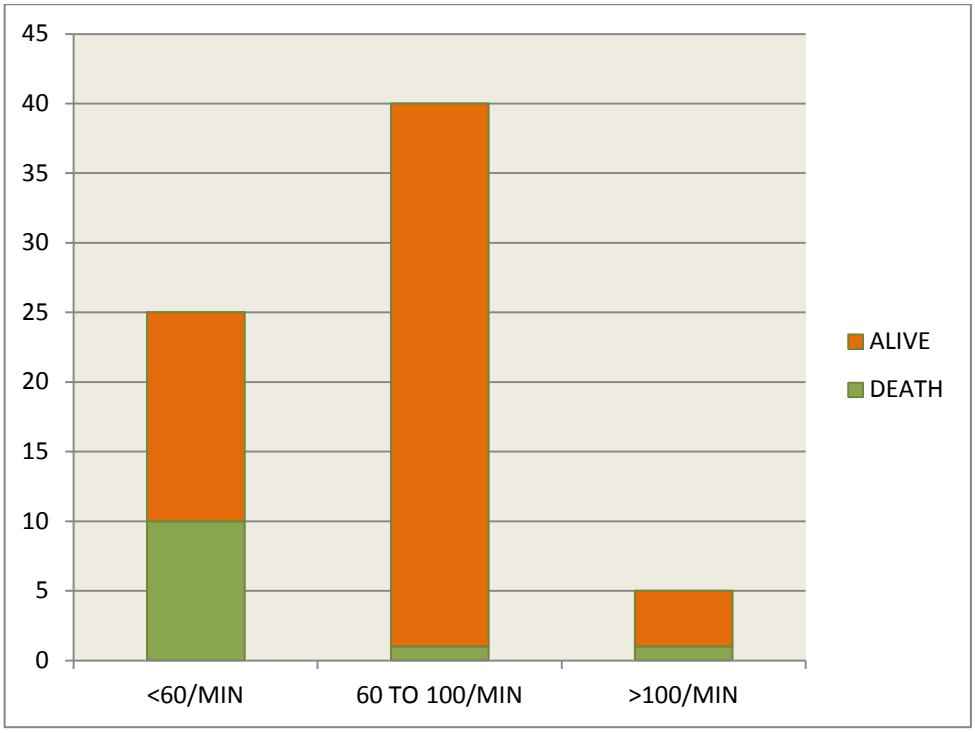


TABLE 17: COMPARISION OF OUTCOME WIYH RESPECT TO SYSTOLIC BLOOD PRESSURE

SBP mm hg	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
BELOW 90 mm Hg	10(83.3%)	13(22.4%)	23(32.9%)	X^2=17.472 DF=2 .000<0.05 SIGNIFICANT
90 TO 120 mm Hg	1(8.3%)	40(69%)	41(58.6%)	
ABOVE 120 mm Hg	1(8.3%)	5(8.6%)	6(8.6%)	

The mortality is more if the initial systolic blood pressure is less than 90 mm Hg that is proven statistically with chi square test. AS FOR ANY ILLNESS SBP LESS THAN 90 MMM HG PLAYS A MAJOR ROLE IN DETERMINING THE OUTCOME OF THE PATIENT .

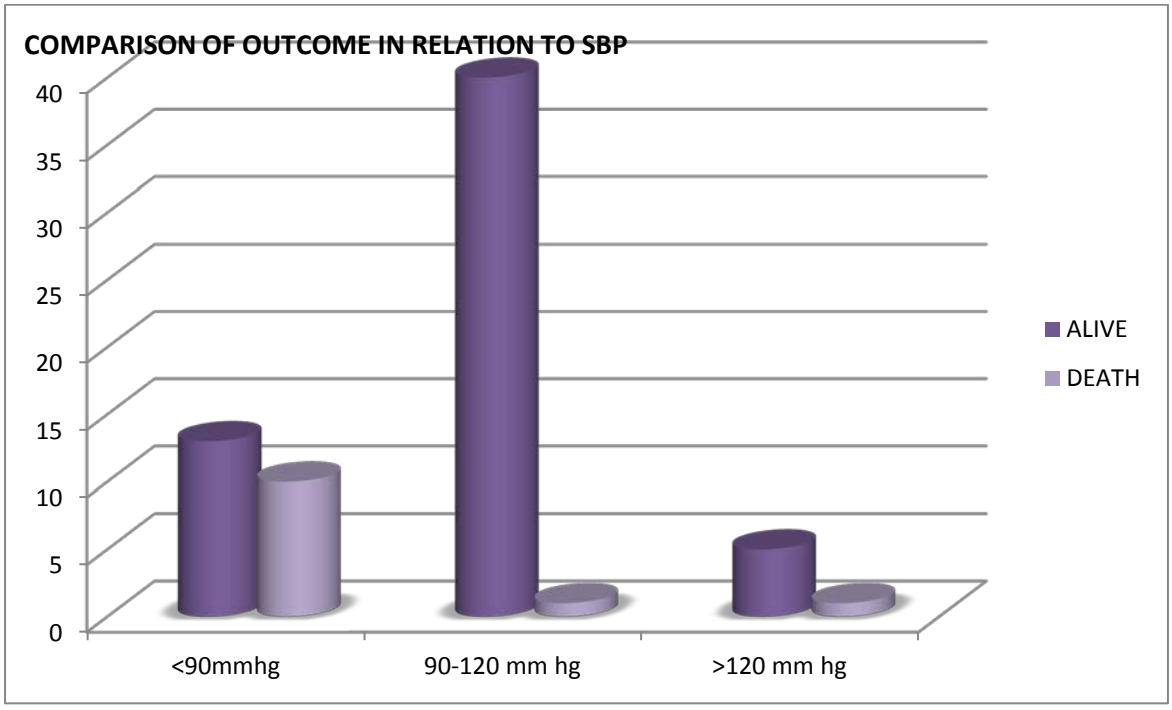


TABLE 18: COMPARISON OF OUTCOME IN RESPECT TO SODIUM LEVELS

NA 2+ mEq/L	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
BELOW 135 mEq/L	1(8.3%)	12(20.7%)	13(18.6%)	X^2=1.332 DF=2 .514>0.05 NOT SIGNIFICANT
135 TO 145 mEq/L	9(75%)	34(58.6%)	43(61.4%)	
ABOVE 145 mEq/L	2(16.7%)	12(20.7%)	14(20%)	

THE TABLE COMPARED THE OUTCOME OF THE PATIENTS WITH THEIR SODIUM LEVELS IN THREE CATEGORIES: NORMAL, HYPONATREMIA & HYPERNATREMIA .

THE TABLE REVEALED **THERE IS NO ASSOCIATION BETWEEN THE OUTCOME AND SODIUM LEVELS**, INSPITE OF HYPONATREMIA BEING A INDEPENDENT PREDICTOR OF MORTALITY IN ICU PATIENTS.

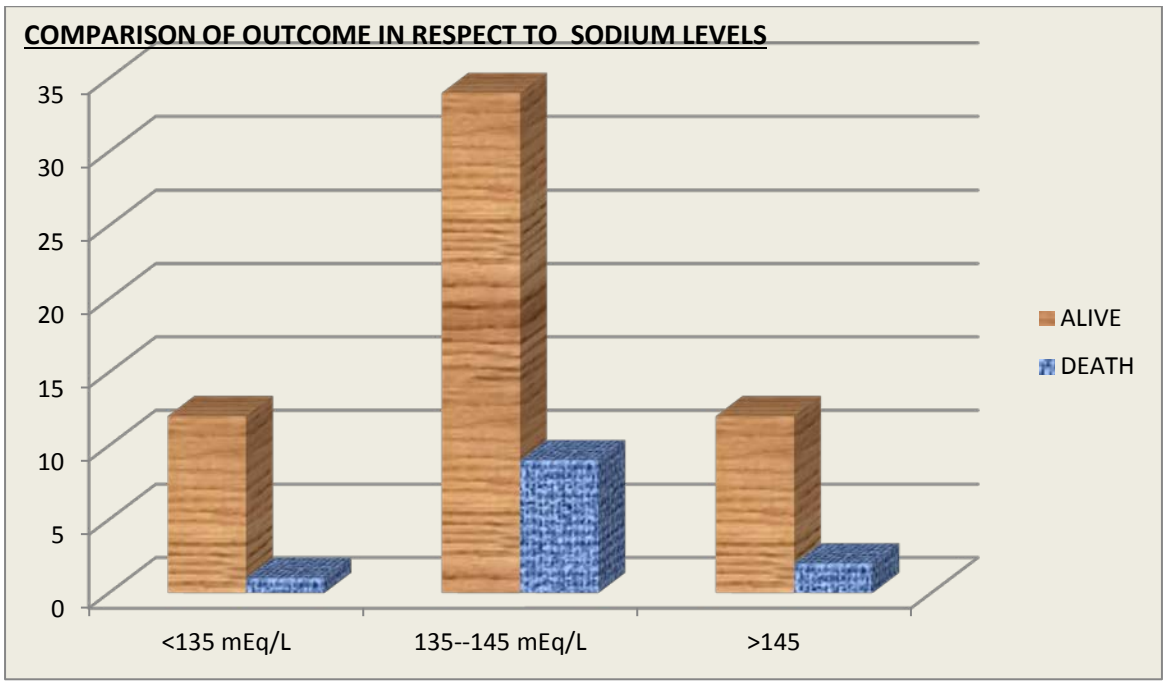
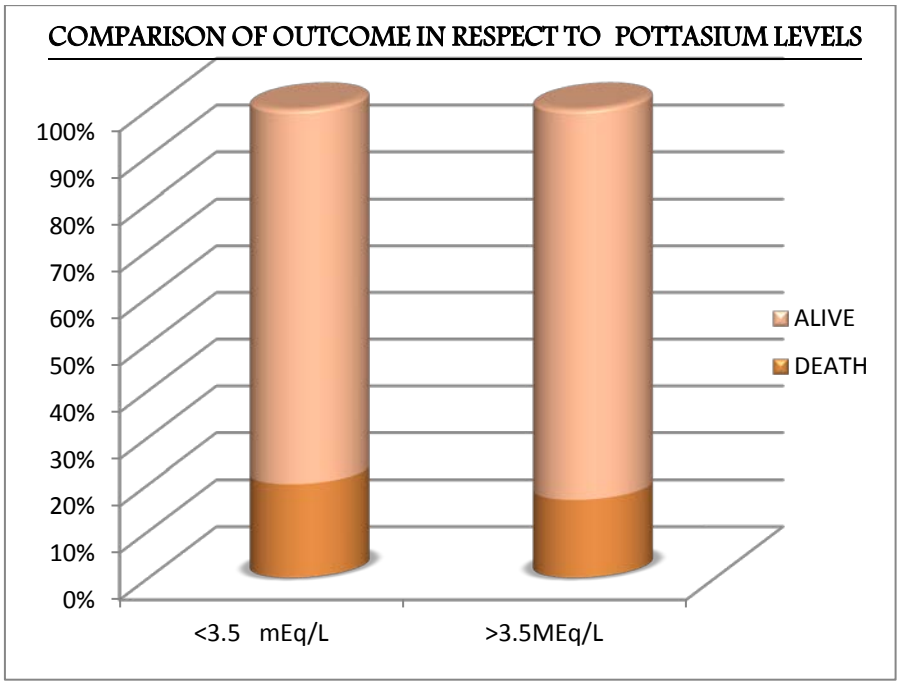


TABLE 19 : COMPARISON OF OUTCOME IN RESPECT TO POTTASIUM LEVELS

K+	OUTCOME			STATISTICAL INFERENCE
	DEATH (N=12)	ALIVE (N=58)	TOTAL (N=70)	
BELOW 3.5	2(16.7%)	8(13.8%)	10(14.3%)	X^2=.067 DF=1 .796>0.05 NOT SIGNIFICANT
ABOVE 3.5	10(83.3%)	50(86.2%)	60(85.7%)	



THE GRAPH INDICATES THAT POTTASIUM LEVELS HAVE NOT SIGNIFICANTLY ASSOCIATED THE OUTCOME OF THE PATIENTS.

STATISTICALLY ALSO THESE CHANGES ARE FOUND TO BE SIGNIFICANT.

TABLE 20:

QTc interval in the group is classified in to three groups: normal <430 msec; intermediate 431—450 msec ; prolonged >450.

The number of patients in each group are given in the table as well as in chart format below.

QT c INTERVAL IN msec	NO OF PATIENTS	PERCENTAGE
<430 msec	21	30%
431 to 450 msec	6	8%
Above 450 msec	43	62%

GRAPH 18:

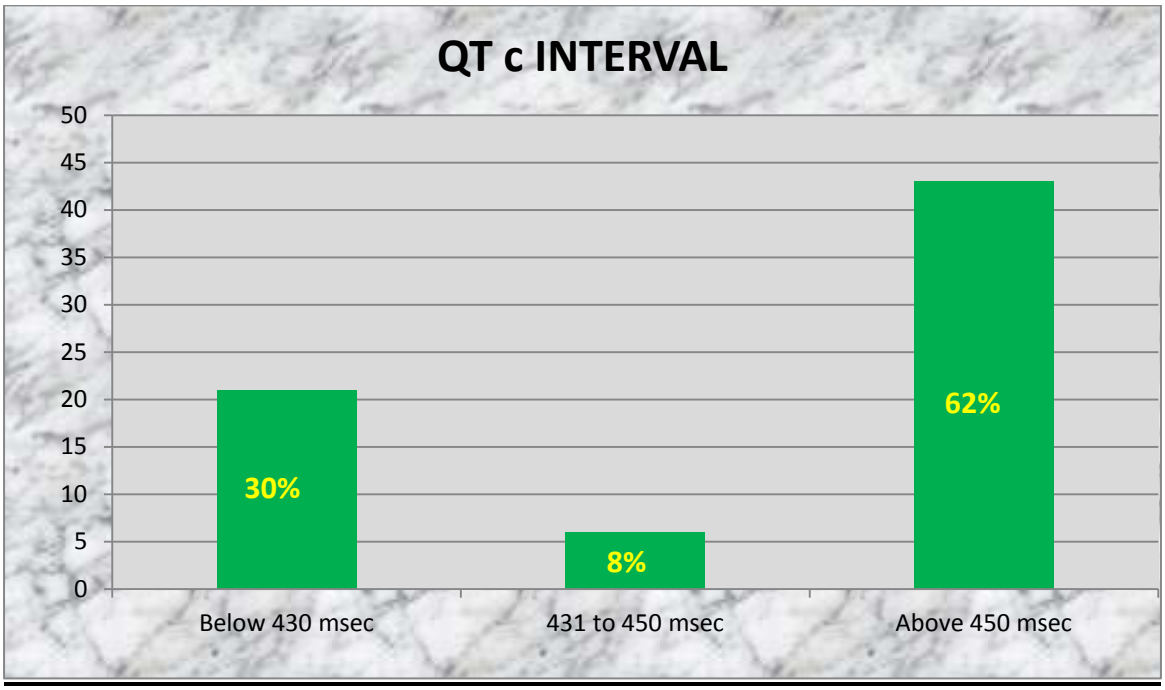


TABLE 21:

QTc interval in millisec	Outcome		
	Alive (n=58)	Death (n=12)	**Total (n=70)**
<430 msec	18	3	21(35%)
431 to 450msec	6	0	6(10%)
Above 450msec	26	7	33(55%)

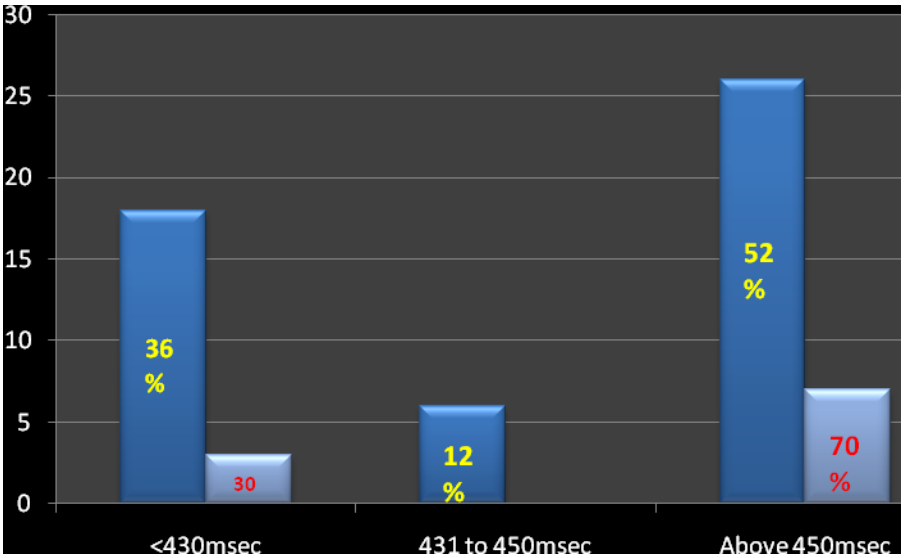
This table shows the number of males with prolonged QTc is 33. Among that mortality rate is 21 % compared to a rate of 14% in those who having <430msec.

Where there is no such difference noted in the female sex.this is shown in the following table.

TABLE 22:

QTc female	**Outcome**		
	Death (n=2)	**Alive (n=8)**	**Total (n=10)**
Above 450	2(100%)	8(100%)	10(100%)

QT c INTERVAL DISTRIBUTION OF ALIVE & DEATH MALE:



Among the 10 death in males , 7 death i.e) 70% death have QTc more than 450 milliseonds.

In those with QTc <430 milliseconds the number of death is 3.

Where there is no such gross variability noted in females.

TABLE 23:

Overall QTc interval in milliseconds	Outcome			Statistical inference
	Death (n=12)	Alive (n=58)	Total (n=70)	
Below 430 msec	3 (25%)	18(31%)	21(30%)	X^2=16.577 Df=2 .041<0.05 Significant
431 to 450 msec	0	6(10.3%)	6(8.6%)	
Above 450 msec	9(75%)	34(58.6%)	43(61.4%)	

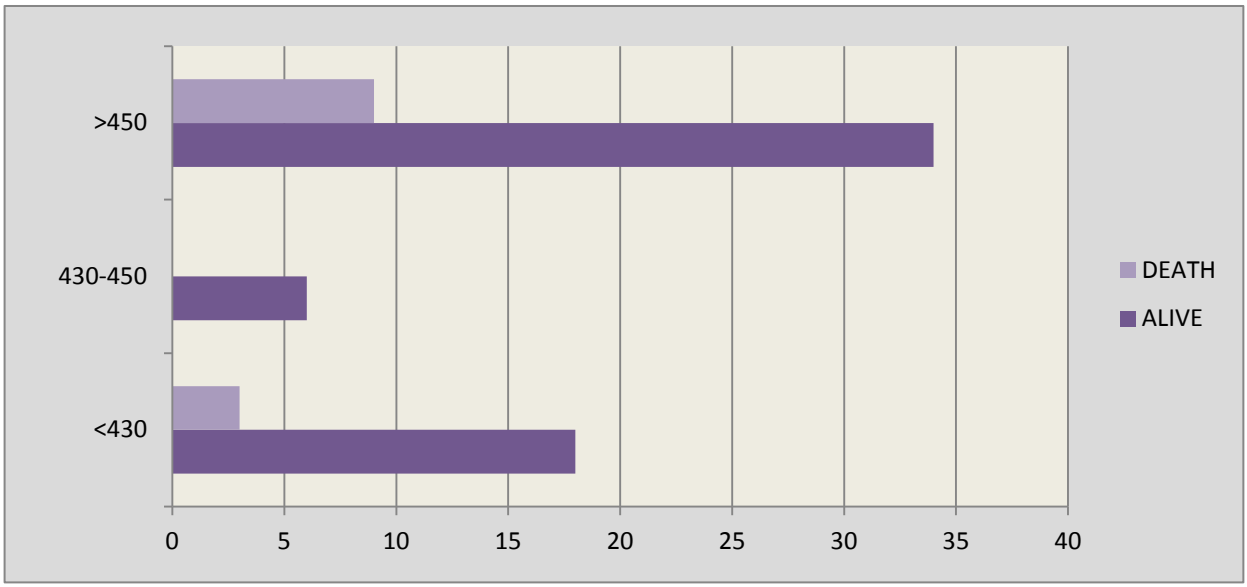
The total number of patients with normal QTc is 21 which constitutes about 30% total population , those with borderline QTc is 6 which is about 8.6% of study population. Those with prolonged QTc is 43 which occupies about 61.4% of the total study population.

Among the total death in the study population,75% are in the group with prolonged QTc , only 25% in the normal QTc group.

This difference in mortality rate among this 2 groups are significantly higher as evidenced by the chi square test with a Df=2.

Thus proven statistically significant.

In this graph Y axis shows QTc in milliseconds which is graded in to three categories as normal, intermediate, increased. Then number of patients who are alive and death are plotted against it which gives the following bar graph. Comparitively death are high in those with prolonged QTc as evidenced statistically also.



DISCUSSION

SEX DISTRIBUTION:

In our study 85% poisoning cases are males , remaining 15% females with suicidal intention (95%) being commoner in both sexes.

This type of sex distribution is seen in most of the studies. One such study is a study conducted a study in a civil hospital by Agarwal[56], V Bhatnagar et al., regarding OPC poisoning in India.

Their study enrolled 65.3% males and 34.7% females. They also noticed that suicidal and intentional poisoning being common as recorded in 80.2% cases followed by occupational (9.1%), accidental (6.6%), homicidal (1.6%) and unknown (2.5%).

TIME LAG FOR ADMISSION:

In our study the time lag between the poison consumption & time of admission plays a major predictor in predicting the mortality. We compared two groups those who arrived before 4 hours with those who arrived late. Even the mortality was higher in the later group , this was statistically significant. But there are many compounding factors like the amount of poison , the nature of the consumed compound which might have influenced the outcome.

Kundu et al., conducted a study at Burdwan Medical college Hospital to identify the predictors of mortality in OPC poisoning patients and found out that increased time interval before hospitalization were associated with higher mortality.

NATURE OF THE COMPOUND:

OPC compounds are available in different chemical mixture in plenty of pesticides. In our study the most common compound encountered is Chlorpyriphos , followed by Monochrotophos then Methyl parathion followed by Dimethoate & Quinophos.

No exact studies in India have analyzed the mortality from the nature of each particular compound. Eastern studies has shown similar results.[58]

In our study apart from other predictors the compound also plays a major role in moratlity with Monochrotophos being the most lethal one contributing to 60% of the mortality.

HEART RATE:

In our study most of the patients presented with normal heart rate (57%), followed by bradycardia then tachycardia. But most of the studies conducted in North India have documented that sinus tachycardia is the most common abnormality encountered even before atropinisation. They have not correlated the pulse rate with the mortality.

In our study the mortality rate has been compared with those presenting with rate less than 60 and those with above rate of 60.

The mortality rate remained significantly higher in group with bradycardia, which has also been proved as statistically significant by chi square test.

BLOOD PRESSURE

Blood pressure variation is also a part of cardiovascular manifestation of OPC poisoning.

Madhur et al., [59]reported that hypotension is more common than hypertension, where as Saadeh AM et al., concluded that hypertension is more common. But there is a chance of getting both in case of OPC poisoning.

In our study 33 % had SBP below 90 mm Hg &59 % had SBP from 90-120 mm Hg .

SBP < 90 mm hg is a indicator of poor outcome which has been proved statistically significant in our study.

SERUM ELECTROLYTES

Almost 60 % in our study had normal sodium level. 20% had sodium below 135 mEq/L and another 20% had above 145 mEq/L.

Regarding potassium level only 15 % had hypokalemia. Remaining all other had normal potassium levels.

Similar results were obtained in the study done by Ludomirsky et al.,[55]

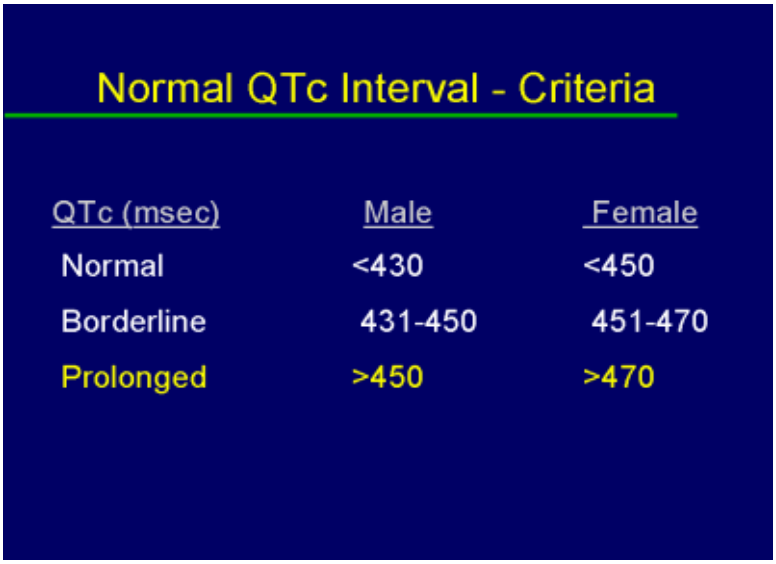
In our study there is no statistical correlation between the electrolyte disturbances and mortality or any other complication.

ECG CHANGES

COMPARISON OF QTc INTERVAL WITH OUTCOME IN OUR STUDY.

QTc interval varies with respect to sex and other physiological variation as described in the review of literature.

Based on electro cardiology society guidelines QTc interval is classified in to normal ,intermediate, increased.



In our study group there are 70 patients including both males and females.

There are no much significant difference in QTc interval in our study with respect to the sex of the individual.

This loss of difference in QT interval may be attributed to wide range in sex distribution, 85% males & 15% females. No study has compared the QTc interval variation in gender aspect.

The total mortality rate in our study is 17 % which is comparatively quite low compared to western and European studies where the incidence of OP poisoning itself is rare when compared to ours.

In our study 62 % of the study population had prolonged QTc. 8 % had borderline QTc . 30 % had normal QTc.

In our study 43 patients had prolonged QTc out of which 33 are males who occupies 55% of the male population. 10 are females. Remaining 22 males had normal QT c interval who occupies 35% population. 6 males remain in the borderline.

Among the 10 death in males, 7 had prolonged QTc i.e) 70 % of the death.
3 had normal QTc.

Almost all the females had QT c more than 450 milli seconds out of which 2 died.

Irrespective of the sex of the individual when compared prolonged QTc with outcome there is a statistically significant difference.

75% of the total death (i.e 9 out of 12) comes under the group with prolonged QTc

25% of death occur in normal QTc group(3 out of 12).

This has been statistically proven by chi square test. X^2 =16.57; Df =2

0.041<0.05 Thus statistically significant.

The following studies are comparable to our results.

DALVIN CP et al., from SETH GS Medical college analyzed the initial electrocardiographic changes of patient admitted with organophosphorus poisoning. According to them abnormal ST-T changes and fall in voltage are the most probable prognostic indicators

Even if clinical recovery is found such patient with ST-T changes should be monitored continuously till the changes recovered Usually most of the changes recover at the time of discharge .with intensive monitoring the mortality rate is reduced from 20% to 4%.

SHADNIA S et al., [65] studied the prognostic importance of QTc prolongation in assessing the severity of lesion. In patients admitted with history of OP poisoning in the casualty were taken cholinesterase and QTc interval was calculated from the initial ECG before atropinization.

It has been already proven in lot of studies that cholinesterase was a prognostic indicator in OP poisoning. Now the patients with normal enzyme levels and decreased enzyme levels are compared with QT interval.

It has been concluded that QTc prolongation can also be compared to serum CE levels. So it can be used as a alternate indicator to asses the severity of poisoning.

More over the atropine requirement was also increased in the group with prolonged QTc.

S.AGARWAL et al .,[56] from BJM Pune quoted that 38% had ECG abnormalities with common being the Sinus tachycardia changes followed by ST-T, then sinus bradycardia.

Paul UK et al.,[60] who done in a cross sectional study at MGM on OPC poisoning patient concluded that prolonged QTc was the commonest electrocardiographic changes followed by sinus tachycardia followed by sinus bradycardia , tachycardia. ventricular tachycardia was found in 5.6%.All the patient`s electrocardiographic changes returned to normal before discharge.

KARKIP et al.,[61] in Singapore evaluated the cardiac complication of organophosphorous poisoning and found out that cardiac complication are common during the initial course of poison intake, but they supported the fact that they are secondary to hypoxemia or acidosis and electrolyte abnormalities.

ANAND et al.,[62] from Philadelphia studied cardiac both at the time of admission and correlated with the necrobiopsy finding .there was found that myocardial involvement is a result of direct toxicity.

SAADEH AM et al .,[63] conformed that prolonged QTc was most common followed by ST-T changes then sinus tachycardia followed by sinus bradycardia.

CHUANG FR et al[64]**.,** in a study done in their EMD dept regarding QTc prolongation in organophosphate poisoning. They compared two groups one with qt prolongation other without QTc prolongation. Patients with prolonged QTc interval are found to have increased mortality (30% Vs 9%) ,increased rate of respiratory failure (80% Vs 35%). So it is proven that complications of OPP are more in the group with prolonged QTc.

So it is necessary to take a electrocardiogram in the casualty before treatment to predict the prognosis.They also compared the severity with cholinesterase level ,in which they concluded that those who come under severe group also had QTc prolongation.

JANG SW et al., conducted a retrospective study on Electrocardiographic findings of organophosphate intoxication in casualty. There are 2 groups. The group with prolonged QTc, the mortality incidence of respiratory failure and frequency of VPC compared with those patients without QTc prolongation. The overall mortality rate and respiratory failure rate were significantly higher. They also found that apart from prolonged QTc the increased frequency of VPC itself is a independent predictor of mortality in OPC poisoning.

SINGH et al.,[66] Conducted a study on the electrocardiographic and clinical features

of parathion poisoning in Punjab. Most of them had sinus tachycardia and other had sinus bradycardia, transient premature supraventricular beats , premature ventricular contractions , RBBB ,ST depression , suggestive of ischemia which reverted to normal with recovery of the patient.

CHHABRA et al., [67] In India studied the ECG changes in patients of malathion poisoning. ECG changes observed in 37 % included intraventricular conduction disturbances and ST-T change.

LUZHNIKOV et al.,[68] from Moscow reported severe organophosphates Poisoning with ECG changes. Patients had various arrhythmias and conduction abnormalities, also had prolonged QT interval, correlating with severity of intoxication and decrease of cholinesterase activity in serum. Patient who exhibited multifocal VPC which degenerated rapidly into ventricular fibrillation. Some patients had atrioventricular and/ or intraventricular conduction disturbances.

KISS AND FAZEKAS et al.,[69] conducted a study on correlation of severity of patients with organophosphorus poisoning with ECG changes within 1-20 days of exposure. They included prolongation of QT interval and ST-T changes. Most of the patients had multiple premature ventricular beats, ventricular

tachycardia, and ventricular fibrillation. Some patients had Bradycardia, idioventricular rhythm.

LUDOMIRSKY et al,.from Israel had noticed that relatively high occurrence of 'torsade de pointes' ventricular tachyarrhythmias in patients intoxicated organophosphate. QT interval prolongation was observed in 14 out of 15 patients. In 6 of these patients 'torsade de pointes' was observed within 4 hours , until 5 days following exposure and they also demonstrated the advantage of treatment with electrical pacing/ isoproterenol as compared with other medical measures.

CHUANGE et al.,from Taiwan conducted a study on ECG changes

which included QTc prolongation in organophosphorus poisoning over 12 years. They found that QTc prolongation in 43.5% patients ,also had higher

mortality (19.6%) and higher incidence of respiratory failure. QTc prolongation also correlated with severity of poisoning.

MANOJITH MUKHERRJEE et al.,[70] from West Bengal conducted a retrospective analysis of patients who were admitted over 8years period with diagnosis of organophosphate poisoning .They observed cardiac arrhythmia in 52%, prolonged QTc in 46%, ST-T changes in 49%, conduction defects in 5%, premature ventricular contractions in 67%.some patient had ventricular tachycardia ,hypotension ,heart failure.

LCH Tsoi et al., assessed the ECG features of OP poisoning. He published the case series and insisted regarding cardiac manifestations of poisoning. Among the manifestations hypotension and bradycardia was common. Around 67 % had prolonged QT interval ,only 9 % had first degree heart block.

VIJAYAKUMAR S et al.,**71** in his prospective study on OP poisoning ECG Findings found that 12 patients had QT >0.43 sec , 8 patients had ST segment elevation and inverted T wave.

CONCLUSION

- OF THE SEVENTY OP POISONING CASES 6O ARE MALES ;10 ARE FEMALE.
    - MALE FEMALE RATIO IS 6:1. THERE IS **NO STATISTICAL SIGNIFICANCE OF GENDER IN MORTALITY** PREDICTION.
- MOST COMMON MODE OF EXPOSURE IS **ORAL INTAKE** & THE INTENTION IS MOSTLY **SUICIDAL.**
- 63% OF THE PATIENTS ARRIVED TO THE HOSPITAL AFTER 4 HOURS. THIS **TIME OF ARRIVAL HAS SIGNIFICANT ROLE IN PREDICTING THE MORTALITY.**
- MOST COMMON COMPOUND CONSUMED IS **MONCHROTOPHOS** (31.4%) FOLLOWED BY CHLORPYRIPHOS (27.2%), METHYL PARATHION (22.8 %) METHYLPARATHION (11.4%) LEAST COMMON IS QUINOPHOS (7.1%).
    - THIS COMPOUND HAS A SIGNIFICANT INFLUENCCE IN MORTALITY WITH **MONOCHROTOPHOS & CHLORPYRIPHOS BEING MOST TOXIC.**
- MOST COMMON PRESENTING SYMPTOM IS **SWEATING** (82%) FOLLOWED BY LOOSE STOOLS (68%) THEN DYSPNEA IN 62 %.
- MOST OF THE PATIENTS IN THE STUDY HAD NORMAL PULSE RATE. ONLY SEVEN PERCENT HAD TACHYCARDIA.BUT THE **MORTALITY RATE WAS HIGHER IN THOSE WITH BRADYCARDIA**.

- SIMILAR TO PULSE RATE ,THOSE WHO PRESENTED WITH **SBP <90 MM HG HAD A POOR OUTCOME** AS PROVEN STATISTICALLY.

- 26 % IN OUR STUDY NEED VENTILATORY SUPPORT & **IT INDIRECTLY INDICATES A POOR OUTCOME .**

- EVEN THOUGH MILD ALTERTIONS ARE THERE IN THE **ELECTROLYTE LEVELS(SODIUM AND POTTASIUM), THERE IS NO STATISTICAL CORRELATION WTH THE MORTALITY**.

- 62 % OF PATIENTS IN THIS STUDY HAD QTc MORE THAN 450 MILLI SECONDS. NORMAL GENDER VARIATION IS NOT OBSEVED IN OUR STUDY.

    - GROUP WITH PROLONGED QTc CONTRIBUTES TO 58.6 % OF THE MORTALITY.
    - SO PROLONGED QTc ITSELF IS IS A SIGNIFICANT PREDICTOR OF MORTALITY IN ORGANOPHOSPORUS POISONING PATIENTS.
    - SO EARLY DETECTION OF QTc PROLONGATION IN ECG AND INITIATION OF EARLY INTENSIVE TREATMENT FOR OPC POISONIG MAY REDUCE THE MORTALITY.

So the main purpose of the study is to tell that electrocardiogram being

1. easily available, affordable bed side investigation it gives us valuable information in predicting the mortality earlier. Thereby increasing the level of care and intensification of treatment.

2.It is advisable to calculate QT c interval in every patient of OPC poisoning instead of relaying on costlier cholinesterase in predicting mortality even it has its own advantages.

ANNEXURE 1

BIBILIOGRAPHY

1. Jeyaratnam.J Acute Poisoning: A major health problem. World Health Stat Q 1990; 43:139-45.

2. Siwach.S.B. Organophosphorus poisoning- newer challenges. Association of Physicians of India Medicine Update 1998; 8: 117-121.

3. Asa Bradman et al.., Variability of Organophosphorous Pesticide Metabolite Levels in Spot and 24-hr Urine Samples Collected from Young Children during 1 Week *Environ Health Perspect*;

4. A. M. Saadeh, N. A. Farsakh, M. K. al-Ali Cardiac manifestations of acute carbamate and organophosphate poisoning. *Heart* 1997;77:461-464

5. Juliana P. DeCarvalho (Feb 28, 2013) History of Toxicology

6.Petroianu GA et al., The synthesis of phosphor ethers: who was Franz Anton Voegeli? Pharmazie. 2009 Apr;64(4):269-75

7. Stedman, E., and Barger, G., *J. Chem. Soc.*, 247 (1925). *Nature* 241, 277 (26 January 1973).

8. Bernard Charles Saunders ; Some aspects of chemistry and toxic action of organic chemicals containing phosphate and fluoride.

9. Dr Timothy T. Marrs, Bryan Pesticide Toxicology and International Regulation page 194

10. Bryan Ballantyne, Timothy C. Marrs Clinical and experimental toxicology of organophosphates and carbamates page 140

11. World Health Organization. WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2001. Geneva: World Health Organization; 2001. WHO/PCS/01.4.

12. Bardin P G, van Eeden S F et al., Organophosphate and carbamate poisoning. Arch Intern Med 1994; 154:1433–41.

13. Kamath PG et al., diazinon poisoning JAPI 1964 12:475

14. Sunder ram J et al., high dose of atropine infusion in op poisoning. JAPI 1991 39(2) 191-93

15. Singh et al., JAPI 1984 181-7 .

16. Maria Konieczny , George Sosnovsky et al., *Chem. Rev.*, 1981, *81* (1), pp 49–7 Chemistry of organophosphorus compounds containing the peroxide bond.

17. IPCS, Monocrotophos Health and Safety guide, No. 80, IPCS International Programme on Chemical Safety, UNEP and ILO, WHO, Geneva, 1993.

18. EPA Pesticide Fact Sheet No. 72, US Environment Protection Agency, 1985

19. EPA 738-F-01-006 February 2002 Chlorpyrifos Facts sheet.

20. IPCS INCHEM DATA SHEETS ON PESTICIDES No. 75

21. Kinkaid.J.C. The Autonomic Nervous System. Medical Physiology,2nd ed.P.108-118.

22.Katzung.B.G, Masters.S.B, Trevor.A.J, Basic & Clinical Pharmacology, McGraw-Hill Medical; 11 ed

23.Wadia RS et al, neurological manifestations of OP poisoning JNeurol Neurosurg Psychiatry1974;37:841- 847

24. Senanayake N, Karaliedde L. Neurotoxic effects of organophosphorus insecticides and intermediate syndrome. N Engl J Med 1987;316:761-3

25. Tsao TC, Juang Y, Lan R, Shieh W, Lee C. Respiratory failure of acute organophosphate and carbamate poisoning, Chest 1990;98:631-6.

26. Dagli AJ et al., pancreatitis involvement in anticholinesterase poisoning british journal of clinical practice 1983;270-72

27. Hsiaso et al., acute pancreatitis following OP poisoning ;journal of toxicology 1996;34;343-47

28. Hui KS et al., Metabolic disturbances In OP poisoning Arch Pathol Lab Med 1983;107(3);154.

29. Matsumiya N et al, Elevated amylase is related to respiratory failure in OP poisoning ; Human Experimental Toxicology 1996;250-53

30. Nk Sundaray, Ratheesh Kumar J, *Trivandrum* Organophosphorus Poisoning:Current Management Guidelines API Medicine Update.

31. Senanayake N[1], de Silva HJ, Karalliedde L. A scale to assess severity in organophosphorus intoxication: POP scale. Hum Exp Toxicol.1993 Jul;12(4):297-9.

32. Bardin P G, Van Eeden S F, Moolman J A, Foden A P, Joubert J R Organophosphate and Carbamate poisoning. Arch Intern Med 1994; 154:1433-41.

33. Dreisbach RH. Cholinesterase inhibitor pesticides. In : Hand Book of poisoning 11th ed. Longe medical publications.California. 1983: 106-14.

34. Samuel J, Thomas K, Jeyaseelan L, Peter JV, Cherian AM. Incidence of intermediate syndrome in organophosphorus poisoning. Assoc Physicians India 1995;43:321-3.

35. De Bleecker J, Van Den Neucker K, Colardyn F. Intermediate syndrome in organophosphorus poisoning: a prospective study.

Crit Care Med 1993;21:1706-11.

36. Peter S, Alexander M, Jeyaseelan L, Cherian AM. Electrophysiological study in organophosphorus poisoning

37. Marion Ehrich and Bernard S. Jortner Organophosphate-Induced Delayed Neuropathy *From:* Handbook of Neurotoxicology, vol. 1 *Edited by:* E. J. Massaro Totowa, NJ

38. Cavanagh, J. B. (1954) The toxic effects of tri-*ortho*-cresyl phosphate on the nervous system. An experimental study in hens. *J. Neurol. Neurosurg. Psychiatry* 17, 163–172.

39. Vilanova, E., Escudero, M. A., and Barril, J. (1999) NTE soluble isoforms: new perspective for targets of neuropathy inducers and promoters. *Chem. Biol. Interact.* 199-120,525–540.

40. The **Agency for Toxic Substances and Disease Registry (ATSDR)** Cholinesterase Inhibitors: Including Insecticides and Chemical Warfare Nerve Agents Part 2: What are cholinesterase inhibitors?

41. [1]Devanur R.M.M. Prasad asian pacific journal of medical toxicology **R**elevance of Plasma Cholinesterase to Clinical Findings in Acute Organophosphorous Poisoning Article 7, Volume 2, Issue 1, March 2013, Page 23-27

42. Aaron C K, Howland M A. Insecticide: Organophosphates and Carbamates. Goldfrank Toxicological Emergencies, Gold Frank L.R., Flomenbaum NE et al, 6th edition, Appleton and Lange, 1998, page1429-1449

43.Vasanaik M. Organophosphate and organocarbamate poisoning-Controversies
in management. The Indian Practitioner 2001;54:340-346.

44. Darren M Roberts, Cynthia K Aaron. Management of Organophosphorus Pesticide poisoning. BMJ 2007; 334; 629-634.

45. Shankar P S. Emergency management of poisoned patient. JAPI 1997; supplement- 2 medical emergencies 14-17.

46. Haddad LM. Organophosphates and other insecticides. In: Haddad LM, Winchester J, editors, Clinical management of poisoning and drug overdose. New York: Saunders; 1990. pp. 1076-87

47. Bardin PG, Van Eden SF. Organophosphate poisoning: grading the severity and comparing treatment between atropine and glycopyrrolate. Crit Care Med 1990;18:956-60

48. Namba T. Cholinesterase inhibition by organophosphorus compounds and its clinical effects. Bull WHO 1971;44:289-307.

49. MA Cherian, C Roshini, JV Peter, AM Cherian Oximes in organophosphorus poisoning Indian journal of critical medicine Year : 2005 | Volume : 9 | Issue : 3 | Page : 155-163.

50. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev 2003;22:165-90

51. Jokanović M[1], Maksimović M A comparison of trimedoxime, obidoxime, pralidoxime and HI-6 in the treatment of oral organophosphorus insecticide poisoning in the rat.

52. Y. Bentur, I. Nutenko, A. Tsipiniuk, B. Raikhlin-Eisenkraft and U. Taitelman

Pharmacokinetics of Obidoxime in Organophosphate Poisoning Associated with Renal Failure1993, Vol. 31, No. 2 , Pages 315-322

53.Elibet Chávez Gonzále The QT interval, its origin and importance of the knowledge of formulas for its measurement in different clinical circumstances *CorSalud 2014 Jan-Mar;6(1):79-85 Cuban Society of Cardiology*

54. Beata Sredniawa MD, Agata Musialik-Lydka MD, Piotr Jarski MD et al.,Indian Pacing Electrophysiol. J. 2005;5(3):221-232 Methods of Assessment and Clinical Relevance of QT Dynamics

55. Achiyahu Ludomirsky, MD, Herman O. Klein, MD et al., Q-T prolongation and polymorphous (“torsade de pointes”) ventricular arrhythmias associated with organophosphorus insecticide poisoning The American Journal of

Cardiology Volume 49, Issue 7, May 1982, Pages 1654–1658

56. S Agarwal, V Bhatnagar, A Agarwal, U Agarwal, K Venkaiah, S Nigam, S *Kashyap internet journal of toxicology* Impairment in Clinical Indices in Acute Organophosphate Insecticide Poisoning Patients in India

57. Goel A., Joseph S. Dutta T.K Organophosphate poisoning: predicting the need

for ventilator support. JAPI 1998;46:786-790.

58.. Karki P, Ansari J A, Bhandary S, Koirala S. Cardiac and Singapore Med J Electrocardiographical manifestations of acute organophosphate poisoning. Singapore Med J 2004;45:385-89.

59. Mathur A., Swaroop A., Agarwal A. ECG changes in acute organophosphorus compound and almunium phosphide poisoning. The Indian Practitioner 1999; 52 ; 248-252.

60. Paul UK, et al. J Indian Med Assoc. 2012 Feb;110(2):98, 107-8.

61. Karki P, et al Cardiac and electrocardiographical manifestations of acute organophosphate poisoning.. Singapore Med J. 2004 Aug;45(8):385-9.

62. Anand S,et al., Cardiac abnormalities in acute organophosphate poisoning. Clin Toxicol (Phila). 2009 Mar;47(3):230-5. doi: 10.1080/15

63. Saadeh AM, et al Cardiac manifestations of acute carbamate and organophosphate poisoning.. Heart. 1997

64. Feng-Rong Chuang, MD, , Shyh-Woei Jang, MD[1],QT_c prolongation

indicates a poor prognosis in patients with organophosphate poisoning The American Journal of Emergency Medicine Volume 14, Issue 5, September 1996, Pages 451–453

65. Shadnia S, Okazi A, Akhlaghi N Prognostic value of long QT interval in acute and severe organophosphate poisoning. J Med Toxicol. 2009 Dec;5(4):196-9.

66. Singh S. , Balakrishna, Satwant singh, Vinod malhotra. Parathion poisoning inPunjab. (A clinical and electrocardiographics study of 20 cases) JAPI 1969;17: 181-187.

67. Chhabra M.L., Sepaha G.C., Jain S. R. et al. ECG and necropsy changes in Organophosphate compound (melathion) poisoning. Indian Journal of Medical science 1970;24:424-429.

68. Luziknov E. A., Savina A. S., Shepelev V.M., on the pathogenesis of cardiac
rhythm and conductivity disorder in case of acute insecticide poisoning. Kardiologica1975;15:126-129.

69. Kiss J, Fazekas T. Arrhythmia in Organophosphate poisoning. Acta cardiol 1979; 34: 323-330.

70. Manojith Mookherjee. Cardiotoxicity profile in organophosphate and carbamate poisoning. Indian Heart Journal 1999; 51: 662.

71. Vijayakumar S, et al. Cardiovasc Toxicol. 2011 A prospective study on

electrocardiographic findings of patients with organophosphorus poisoning.

72. Luziknov E. A et al., on the pathogenesis of cardiac rhythm and conductivity disorder in case of acute insecticide poisoning. Kardiologica1975;15:126-129

ANNEXURE II

PROFORMA

A STUDY ON PROGNOSTIC SIGNIFICANCE OF QTc INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS.

NAME: IP NO:

AGE: DOA:

SEX: DOD/DEATH:

OCCUPATION:

CHEMICAL NAME OF THE COMPOUND CONSUMED:

INTENTION OF POISON CONSUMPTION: ACCIDENTAL / SUICIDAL

TIME SINCE CONSUMPTION:

FIRST AID GIVEN(INCLUDING ATROPINE) OUTSIDE OR NOT:

CLINICAL SYMPTOMS:

	YES	NO
ASYMPTOMATIC		
LOOSE STOOLS		
SWEATING		
BREATHING DIFFICULTY		

PAST H/O:

ANY EVIDENCE OF CORONARY HEART DISEASE Y/N

ANY H/O DRUG INTAKE CAUSING PROLONGED QT INTERVAL Y /

N

H/O TYPE 2 DM/ SHT /BA

EXAMINATION:

CONSCIOUS / DROWSY /IRRITABLE / UNCONSCIOUS

VITAL SIGNS:

PULSE RATE (PER MIN)	<60	60-100	>100
SBP (MM HG)	<90	90-120	>120
RR (PER MIN)	<20	>20	

SPO2: % IN RA

SBC:

NECK MUSCLE WEAKNESS: PRESENT / NOT

MUSCLE FASICULATION: PRESENT /NOT

PUPIL SIZE:

LUNG SIGNS:

LAB INVESTIGATIONS:

1. RBS
2. SR.UREA
3. SR.CREATININE
4. SR.SODIUM
5. SR.POTTASIUM

DURATION OF THE HOSPITAL STAY:

MECHANICAL VENTILATORY SUPPORT NEEDED OR NOT:

NUMBER OF DAYS OF MECHANICAL VENTILATION:

ATROPINISATION NEEDED HOW LONG ?

OUTCOME OF THE PATIENT:

ELECTROCARDIOGRAM:

1. RATE:

2. RHYTHM:

3. PR INTERVAL:

4. QRS DURATION:

5. QT INTERVAL :

6. QT c INTERVAL:

7. ST T CHANGES:

8.PRESENCE OF VPCs:

FINAL IMPRESSION OF THE ECG:

MASTER CHART

S. NO	IP NO	SEX	time	poison	Symptoms				Vitals			Signs			Electrolytes		Hospitalization		ECG		OUTCOME
					NO SYMP	LOOSE STOOLS	SWEATING	DYSNEA	PR / min	SBP mmhg	RR / min	NECK WEAKNESS	PUPIL SIZE (mm)	LUNG SIGNS	NA 2+	K+	ATROPINISED DAYS	VENTILATOR	RATE IN ECG	QTc	
1	29605	M	6	chlor	No	Yes	Yes	Yes	70	110	12	Yes	2	Yes	136	3.5	6	No	75	480	Alive
2	36342	M	4	methyl	No	No	Yes	Yes	64	100	14	No	3	Yes	132	3.8	3	No	60	500	Alive
3	39838	M	8	chlor	No	Yes	Yes	No	78	128	16	No	3	No	136	4	7	No	75	510	Alive
4	36382	M	7	methyl	No	No	Yes	No	64	100	12	No	3	No	128	3.2	3	No	62	440	Alive
5	40546	M	2	methyl	No	No	Yes	No	78	88	12	Yes	3	Yes	130	3	8	Yes	76	480	Alive
6	40502	M	12	chlor	No	Yes	No	No	64	90	12	No	3	No	140	4.1	4	No	65	490	Alive
7	36322	M	6	quino	No	No	Yes	No	82	120	14	No	3	No	134	3.9	5	No	84	410	Alive
8	38704	M	10	quino	No	No	Yes	Yes	80	136	16	Yes	2	Yes	138	2.7	3	No	73	390	Alive
9	40898	M	4	chlor	No	Yes	Yes	Yes	60	120	14	No	4	Yes	136	3.5	5	No	61	500	Alive
10	37140	M	6	methyl	No	No	No	No	68	110	12	No	3	No	132	4	3	No	70	440	Alive
11	40939	M	8	mono	No	No	Yes	Yes	74	126	16	Yes	3	No	130	3.6	4	No	75	500	Alive
12	41348	M	11	chlor	No	Yes	Yes	No	72	122	14	No	3	No	128	3.9	6	No	75	470	death
13	41075	M	10	methyl	No	Yes	Yes	Yes	68	118	12	Yes	3	Yes	134	4.2	7	Yes	69	490	Alive
14	41348	M	8	chlor	No	Yes	Yes	Yes	68	120	18	Yes	2	Yes	136	3	3	Yes	68	400	Alive
15	41000	M	7	mono	No	No	No	No	74	110	16	No	3	No	138	4.1	3	No	75	480	Alive
16	32954	M	4	methyl	No	No	Yes	No	80	96	14	No	3	No	140	4.2	4	No	81	440	Alive

17	32355	M	3	quino	No	Yes	Yes	Yes	58	90	11	Yes	1	Yes	144	4.8	7	Yes	60	500	Alive
18	23862	M	6	chlor	No	Yes	Yes	Yes	60	94	13	No	2	Yes	143	4.3	5	No	62	510	Alive
19	21798	F	5	methyl	Yes	No	No	No	74	90	15	No	3	No	148	4.6	6	No	75	490	Alive
20	23862	F	2	mono	No	Yes	Yes	Yes	62	94	14	No	2	Yes	143	4.7	5	No	60	480	Alive
21	28879	M	5	methyl	Yes	No	No	No	70	100	16	No	3	Yes	144	4.4	3	No	75	436	Alive
22	27990	M	2	chlor	No	Yes	Yes	Yes	72	98	12	Yes	2	Yes	145	4.5	5	No	70	440	Alive
23	30130	F	6	mono	No	Yes	Yes	Yes	56	86	10	Yes	1	Yes	146	4.2	8	Yes	62	550	Alive
24	28251	M	8	mono	No	Yes	Yes	No	74	98	12	No	2	Yes	143	3.8	5	No	73	402	Alive
25	32876	M	4	quino	No	Yes	Yes	Yes	50	80	10	Yes	1	Yes	139	4	9	Yes	51	488	Death
26	28224	M	8	chlor	No	Yes	Yes	No	64	96	14	No	3	No	140	3.7	6	No	72	440	Alive
27	28246	M	3	mono	Yes	No	No	No	86	108	16	No	3	No	138	3.9	3	No	90	402	Alive
28	30141	F	2	methyl	No	Yes	Yes	Yes	56	90	10	Yes	2	Yes	137	3.6	6	No	62	512	Alive
29	34280	M	5	mono	No	Yes	Yes	No	68	110	18	No	2	Yes	139	4	4	No	73	420	Alive
30	32275	F	3	methyl	No	Yes	Yes	Yes	58	100	12	Yes	2	Yes	136	4.1	6	Yes	60	480	Alive
31	29352	F	5	chlor	No	Yes	Yes	Yes	54	90	12	Yes	2	Yes	142	4.6	6	No	60	502	Alive
32	28894	M	7	mono	No	Yes	Yes	Yes	84	100	16	No	3	No	145	4.3	3	No	80	464	Alive
33	29617	M	4	dimeth	No	Yes	Yes	No	70	96	14	No	3	No	138	4	4	No	82	406	Alive
34	33359	M	5	chlor	No	Yes	Yes	Yes	58	90	10	Yes	2	Yes	140	3.8	6	No	63	482	Alive
35	34276	M	5	mono	No	No	Yes	Yes	84	100	16	No	3	Yes	144	3.9	5	No	102	512	Alive
36	36338	M	3	methyl	No	Yes	Yes	Yes	60	90	13	Yes	2	Yes	148	4.4	7	Yes	62	496	Alive

37	30406	M	6	dimeth	No	No	Yes	Yes	80	110	18	No	2	Yes	146	4.6	4	No	84	502	Alive
38	30948	M	4	chlor	No	Yes	Yes	Yes	54	86	10	Yes	1	Yes	148	3.8	3	Yes	61	400	Death
39	33450	M	8	mono	No	Yes	Yes	Yes	64	90	11	Yes	2	Yes	145	3.7	5	Yes	73	509	Alive
40	28248	M	2	mono	No	Yes	Yes	No	72	96	15	No	3	No	146	4.4	5	No	80	496	Alive
41	29270	M	3	dimeth	No	Yes	Yes	Yes	60	100	12	Yes	2	Yes	147	4.5	6	No	64	498	Alive
42	32902	M	5	chlor	No	Yes	Yes	Yes	56	90	12	Yes	3	Yes	154	3.2	5	No	61	410	Alive
43	32004	M	6	mono	No	Yes	Yes	Yes	50	80	10	Yes	2	Yes	143	4.8	7	Yes	64	490	Alive
44	32838	M	5	mono	Yes	No	No	No	88	110	16	No	4	No	145	4.6	5	No	96	406	Alive
45	32341	M	2	methyl	No	Yes	Yes	Yes	78	100	14	Yes	2	Yes	146	4.5	6	No	84	498	Alive
46	32648	F	4	chlor	No	Yes	Yes	Yes	60	100	11	Yes	2	Yes	146	3.8	6	No	61	486	Alive
47	34044	M	6	mono	No	Yes	Yes	Yes	68	126	12	Yes	2	Yes	138	3.7	4	No	75	494	Alive
48	35700	M	5	chlor	No	Yes	Yes	Yes	50	86	8	Yes	1	Yes	139	4.2	6	Yes	54	512	Death
49	35611	M	7	mono	No	Yes	Yes	Yes	46	84	9	Yes	1	Yes	148	2.8	7	Yes	50	494	Death
50	39804	M	6	mono	No	Yes	Yes	Yes	54	90	10	Yes	1	Yes	144	3.8	6	Yes	61	400	Death
51	33873	F	8	dimeth	No	Yes	Yes	No	74	120	12	Yes	3	No	145	4.3	4	No	73	486	Alive
52	35412	M	4	chlor	No	Yes	Yes	Yes	60	100	14	Yes	2	Yes	146	3.8	6	No	60	491	Alive
53	36087	M	5	dimeth	No	Yes	Yes	Yes	64	94	14	Yes	2	Yes	148	4.3	8	No	60	490	Alive
54	36211	M	4	mono	No	Yes	Yes	Yes	50	86	10	Yes	2	Yes	140	3.9	7	Yes	51	502	Death
55	36363	M	7	chlor	No	Yes	Yes	Yes	70	110	13	Yes	2	Yes	144	3.7	5	No	74	500	Alive
56	36381	M	6	mono	No	Yes	Yes	Yes	48	86	10	Yes	1	Yes	143	4.8	6	Yes	50	482	Death

57	39032	M	9	dimeth	No	Yes	Yes	Yes	80	120	14	Yes	2	Yes	148	4.3	6	No	75	494	Alive
58	38626	M	4	mono	Yes	No	No	No	84	126	16	No	3	Yes	145	4.5	3	No	80	470	Alive
59	39371	F	2	chlor	No	Yes	Yes	Yes	44	80	10	Yes	1	Yes	140	4	1	No	50	502	Death
60	41066	F	8	dimeth	No	Yes	Yes	Yes	50	90	11	Yes	1	Yes	138	3.8	1	No	50	492	Death
61	42907	M	6	methyl	No	No	Yes	Yes	52	68	32	Yes	1	Yes	140	3.9	3	Yes	51	412	Death
62	40900	M	2	mono	No	No	No	Yes	68	100	14	No	3	No	136	4	5	Yes	72	420	Alive
63	41469	M	10	mono	No	No	Yes	Yes	74	110	16	Yes	3	Yes	132	5.2	4	No	76	396	Alive
64	40057	M	6	chlor	Yes	No	No	No	76	96	16	No	3	No	128	3.1	6	No	75	394	Alive
65	31453	M	5	dimeth	No	Yes	Yes	No	100	120	12	No	3	No	134	5.4	3	No	100	418	Alive
66	35418	M	12	mono	No	Yes	Yes	No	58	96	14	No	3	No	134	3.5	5	No	60	398	Alive
67	35450	M	6	dimeth	No	Yes	Yes	Yes	72	120	16	Yes	2	No	140	3.6	4	No	72	393	Alive
68	34476	M	4	methyl	Yes	No	No	No	64	100	12	No	3	No	128	3.8	7	No	64	405	Alive
69	35441	M	3	methyl	No	Yes	Yes	No	79	90	12	No	3	No	136	3.8	5	No	82	406	Alive
70	36952	M	8	methyl	No	No	No	No	86	98	12	No	3	No	140	4	6	No	90	390	Alive

ABBREVATIONS

ABG	Arterial Blood Gas Analysis
APD	Action Potential Duration
ARDS	Acute Respiratory Distress Syndrome
AV Node	Atrio Ventricular Node
CNS	Central Nervous System
Camp	Cyclic Adenyl Mono Phosphate
DAG	Di Acyl Glycerol
ECG	Electro Cardio Gram
ENS	Enteric Nervous System
HR	Heart Rate
Ig	Immunoglobulin
IV	Intravenous
K+	Pottasium
Na2+	Sodium
NTE	Neuropathy Target Esterase
OPC	Organo Phosphorus Compound
OPIDP	Organo Phosphorus Induce Delayed Polyneuropathy
PEEP	Positive End Expiratory Pressue
PR	Pulse Rate
PNS	Peripheral Nervous System
RBS	Random Blood Sugar
RR	Respiratory Rate
SA node	Sino Atrial Node
SBP	Systolic Blood Pressure

TDP	Torsades De Pointes
TEPP	Tetra Ethyl Pyrophosphate
TOCP	Tri-Ortho-Cresyl Phosphate
TOTP	Tri-Ortho-Tolyl Phosphate
TSH	Thyroid Stimulating Hormone
Vd	Volume Of Distribution
VPC	Ventricular Premature Complex
VT	Ventricular Tachycardia

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .M.BALAMURUGAN,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

INFORMATION SHEET

We are conducting a prospective study on **A STUDY ON PROGNOSTIC SIGNIFICANCE OF QTc INTERVAL IN THE INITIAL ECG OF OPC POISONING PATIENTS.**

in the Department of General Medicine , Thanjavur Medical College & Hospital, Thanjavur – 613004.

- At the time of announcing the results and suggestions, name and identity of the patients will be confidential.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator **Signature of participant**

Date

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